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ANNALS OF
INTERNAL MEDICINE

VOLUME 13 JULY, 1939 NUMBER 1

VIRUS INFECTION OF THE CHICK EMBRYO*

By ERNEST W. GOODPASTURE, *Nashville, Tennessee*

ALTHOUGH physical and chemical methods, especially the former, are being employed extensively at the present time in efforts to elucidate the size, shape, composition and general properties of the ultimate virus particles, an exact determination of their nature as a class has not yet been arrived at; and it is still necessary to resort to the biological method of infecting susceptible hosts, whether cell-suspensions or organized animals and plants, in order to demonstrate and to study the activity of these agents.

Manifestation of a virus activity involves interactions between it and living susceptible cells, in the course of which virus multiplies and the affected cell undergoes a variety of changes, now recognizable as more or less characteristic and individually specific effects of the active agent concerned.

Such demonstrable changes in cells as hyperplasia, development of cellular inclusions, swelling, degeneration, lysis and necrosis in varying proportions and designs constitute the essential representations of the effect of viruses upon the cells susceptible to them; and the one substantial inference to be drawn by students of viruses from the phenomena presented by infected hosts, and from the negative results of attempted culture on dead media, is that living cells are necessary at present for an increase of viruses in quantity. This induction is substantiated whether one hypothecates that viruses are represented by huge proteid molecules elaborated by the infected cell, or that they are minute parasites. In either event one may further infer that multiplication of virus, in the sense of increase in quantity, occurs in the interior of living protoplasm of susceptible cells.

Experimental demonstration of the presence of active virus in the interior of living cells and in relationship with a specific virus inclusion was made several years ago by C. E. Woodruff and myself in our investigations of the pathogenesis of fowl-pox.[1]

* Read at the Meeting of the American College of Physicians in New Orleans, March 28, 1939.

From the Department of Pathology, Vanderbilt University Medical School, Nashville, Tenn.

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We found that trypsin in weakly alkaline solution would rapidly free the specific cellular inclusions of fowl-pox from infected epithelial cells by dissolving the epithelial membrane and cytoplasm, so that the refractive inclusions, which are relatively quite large and substantial, could be obtained in quantity. By picking out individual inclusions with a micro-pipette and washing them in 2 per cent NaCl solution, until the washings no longer contained demonstrable active virus, we showed that single washed inclusions inoculated into a feather follicle of a hen caused fowl-pox infection at that site. Each well-formed inclusion contains about 50 thousand or more minute particles, uniform in size, coccoid in shape and possessing definite staining reactions. These are incorporated in the inclusions by a lipo-proteid matrix, and they are known as the specific elementary bodies of this disease. By means of an attenuated glass point and a micro-dissector, we were able to break up a single inclusion and to inoculate several feather follicles of a hen with minute fragments containing elementary bodies, and the result was multiple infections with material from one inclusion.[2]

This evidence indicates very strongly that the elementary bodies of the fowl-pox intracellular inclusion are associated with the specific virus of this disease, and that they become agglomerated within the cell into a cytoplasmic mass, together with a lipoproteid matrix, which is known as the Bollinger body, the specific cellular inclusion of fowl-pox. We have likewise demonstrated that the elementary bodies of vaccinia and of molluscum contagiosum are intracellular and are the most important constituents of the respective cellular inclusions.

Other evidence that viruses invade and multiply within cells, especially important from the standpoint of pathogenesis, has been derived from experimental infections with viruses which affect nerve cells.

Several years ago Oscar Teague and I obtained experimental evidence that herpes simplex virus gains entrance into the central nervous system of rabbits and spreads there, through the axis cylinders of peripheral nerves, following a peripheral focal infection. These neural processes are of course prolongations of neuronal cytoplasm, and certain neurotropic viruses seem to multiply and to progress within and along these extended cytoplasmic threads from the periphery to the main body of the nerve cell within the ganglia, brain or spinal cord.[3] More recently evidence has been obtained by us and by others that a similar axonal transmission of the viruses of rabies, poliomyelitis, equine encephalomyelitis, pseudo-rabies and other neurotropic viruses takes place in experimental infections.

It is thus evident that experimental investigation of virus diseases at the present time requires not only susceptible hosts in which serial transmission can be effected, but also the employment of the technics of cytopathology.

The matter of securing suitable susceptible hosts for the study of virus infections is a problem of the very greatest importance and it involves many special considerations, because it is now well known that viruses may behave differently not only in different hosts, but in different tissues of the same

host. As a result of varying the tissue environment a virus may become suddenly or gradually profoundly modified. For example my colleague, G. J. Buddingh, has recently shown that one passage of fowl-pox virus through the brain of a newly hatched chick will cause a strain of this virus, normally restricted almost exclusively in its effects to squamous epithelium, to become highly infectious for cells of the meninges, of the choroid plexus and of cells of mesodermal origin, namely, endothelium and fibroblasts. This change in the virus appears to be a permanent one and manifests itself even when the usual epithelial tissues are inoculated.[4]

Variation by passage through an alien host is illustrated by modification of a strain of the virus of yellow fever, maintained in monkeys, by passage through the brains of mice, first accomplished by M. Theiler, and this change in the virus has resulted in the acquisition of a vaccine useful for human prophylaxis.[5, 6, 7]

There are some disadvantages, however, in using various free living animals as hosts for viruses, because animals so used have been found at times to harbor their own viruses which may contaminate that employed experimentally.

For such and other reasons investigators of virus diseases have felt a need for a host, easy of access, in which virus infections generally, might be induced without contamination by bacteria and other viruses. A host that meets many of the requirements has been found in the chick embryo of developing eggs.

In 1931 A. M. Woodruff and I, in searching for a method by means of which we could obtain fowl-pox in quantity free from bacterial contamination, found that the chorio-allantois of developing eggs is a tissue very susceptible to this virus, and the infections resulting from inoculation with fowl-pox reproduced the characteristic lesions and afforded virus in great abundance free from all contamination by other infectious agents.[8] Buddingh, Woodruff and I later demonstrated that vaccinia and herpes simplex viruses could likewise be cultivated in this tissue in pure strain, notwithstanding the fact that newly hatched chicks are entirely insusceptible to herpes virus and only slightly susceptible to vaccinia.[9] It thus appeared that we had at hand not only a host usually free of complicating infectious agents, but one highly susceptible to a variety of viruses.

Following these reports the embryonic tissues of the developing egg were used by a number of investigators for the purpose of cultivating and studying viruses,[11] and I should like to summarize briefly some of the results that have been obtained.

1. The Susceptibility of the Chick Embryo to Viruses

The cells of the chick embryo have been found to be susceptible to infection by a much greater number of viruses than any other single host. Consequently the embryo may be used as a convenient living medium for the cultivation and experimental investigation of a great variety of these agents.

The following viruses that are pathogenic for man have already been cultivated in this medium, namely, those of small-pox, alastrim and vaccinia; herpes simplex, and virus B., yellow fever and Rift Valley fever; St. Louis encephalitis, lymphocytic choriomeningitis, equine encephalomyelitis, louping-ill of sheep and rabies[10]; the common cold, epidemic influenza and psittacosis.

Of viruses affecting animals but to which man is apparently insusceptible, the following have been cultivated in chick embryos: Rous sarcoma, fowl-pox, fowl-plague, infectious laryngo-tracheitis of fowls, New Castle disease, infectious bronchitis of chickens, Pacheco's parrot disease, vesicular stomatitis of horses, myxomatosis of rabbits, ectromelia of mice, sheep-pox and pseudo-rabies.

Thus far among viruses affecting man the following have resisted cultivation in the chick embryo, namely those of molluscum contagiosum, warts, mumps, herpes zoster, varicella, poliomyelitis and measles.

It has been reported that the virus of measles, for which there is no other adequately proved susceptible host than man, has been cultivated in the chick embryo, but there is as yet no acceptable confirmation. Our own efforts in this direction have thus far resulted in failure. However, with improved technics of inoculation now at our disposal, it seems possible that some of the viruses that have resisted cultivation many prove upon further and more intensive investigation to be infectious for this host. Especially should attempts to infect the embryo with the viruses of poliomyelitis and measles be continued and intensified, for successful results might be of great significance for prophylaxis.

2. The Chick Embryo Method as a Means for Purifying, Separating and Identifying Viruses

It has been of especial interest to us to observe that the tissues of the chick embryo, including the chorio-allantois, are rather resistant to infection by saprophytes and some common bacterial pathogens, so that it is frequently possible to obtain on primary culture in the membranes a bacteria-free strain of virus originally moderately contaminated. G. J. Buddingh, for example, has obtained bacteria-free strains of vaccine virus from primary inoculation of the chorio-allantois with calf lymph, and with material from a vaccine pustule on a child's arm. Last year he cultured a bacteria-free strain of smallpox virus by inoculating a series of membranes with pus removed directly from cutaneous lesions of a case of variola in the thirteenth day of illness.[11]

Galloway and Elford have shown that the viruses of vesicular stomatitis and foot and mouth disease could be readily differentiated and separated from mixed infections by a combination of filtration and growth on the egg membrane.[12]

As to the identification of viruses by the chick embryo technic it is to be said that each virus induces more or less characteristic lesions in its

natural host, and when successfully inoculated into the tissues of the chick embryo the same sorts of cellular changes are reproduced. Burnet furthermore has laid great stress upon the chick embryo technic as a means of titrating virus suspensions following dilution and after incubation with specific immune serum.

3. The Culture of Viruses for Vaccines

G. J. Buddingh and I in recent years have developed a satisfactory method for preparing antismallpox vaccine in quantity, and free of bacteria, by infecting the chorio-allantois of chick embryos. Modifications of this method have been used by others for the same purpose and with satisfactory results. Our own experience has led us to believe that a vaccine thus prepared could with advantage supplant calf lymph for human antismallpox prophylaxis.[12] A recent extensive report by Stevenson and Butler from the National Lymph Establishment is very favorable to its use. By the use of a modified technic, involving injection of virus into the amnion, Buddingh has recently been able to increase the yield of vaccine many fold, so that the tissues of a single embryo would afford a thousand or more standard doses of vaccine.* The method which he has described of preserving such a vaccine in sterile serum not possible with contaminated calf lymph, greatly prolongs its activity even against the adverse effects of body temperature.

Assuming a rôle of immense importance in individual and mass protection against yellow fever, endemic on two continents, are the recently developed methods of vaccination by the use of attenuated strains of yellow fever virus. The strain used by the International Health Division of the Rockefeller Foundation, with which over a million persons have been vaccinated in South America, is propagated routinely in tissue cultures, but for vaccine production it is inoculated into chick embryos. The infected embryos yield an abundance of virus. The vaccine induces a mild infection, without significant clinical symptoms, and is followed by the appearance of antiviral antibodies in the circulating blood signifying protective immunity.

Among the newcomers of viruses discovered to be pathogenic for man is that of equine encephalo-myelitis, now thought to be an endemic infection among a variety of birds rather than a natural disease of horses. There are two immunologically distinct strains of this virus in our country, namely, the Eastern and the Western strains, and during the past year fatal infection with each has occurred in human beings. Both are highly infectious for chick embryos.

J. Beard has described a vaccine prepared from virus cultivated in the chick embryo and treated with formalin, which is being widely used with apparent success in animal prophylaxis.[14] It is to be hoped that human infection with this virus will not reach proportions requiring similar immunizing procedures.

* Personal communication.

F. R. Beaudette informs me that the New Jersey College of Agriculture supervises the production of laryngotracheitis vaccine at the Vineland Poultry Laboratories to insure purity and potency of the product. This virus is grown on the chorio-allantois with excellent results. That laboratory also produces its pigeon and fowl-pox vaccine in the same way, by cultivation in the chick embryos.

4. Infection of Chick Embryos as a Means of Inducing Mutations and Modifications of Viruses

From the standpoint of practical application of prophylactic vaccination against virus diseases it is of great importance to have a means of reducing the virulence of a particular virus so that a mild or inapparent infection might be induced that would leave the host with a protective immunity. This principle is an ancient one of proved worth in Jennerian prophylaxis against smallpox.

With some viruses it is quite possible to reduce the virulence for a susceptible host by repeated membrane to membrane passage in the developing egg. For example Katherine Anderson, in my laboratory, has recently shown that an increase of virulence for the embryos is acquired by a neurotropic strain of herpes simplex virus during repeated egg to egg passage and this increased virulence is associated with a great loss of pathogenicity for the rabbit. After the thirtieth membranal passage the virus causes extensive hepatic and other internal lesions in the embryo, which are not observed with earlier passages, but the strain at this stage had completely lost its ability to cause encephalitis in the rabbit following corneal infection, and the keratitis following corneal inoculation was so mild as to be almost imperceptible. Such a mild infection, however, calls forth substantial immunity of the cornea.[15]

Very promising for an eventual successful vaccine for human epidemic influenza are the results which Burnet and his collaborators have obtained from infection of the chick embryonic membranes with the virus of human influenza.[12] On repeated passage of the " Melbourne " strain of this virus through chick membranes Burnet observed, after the tenth passage, a gradual increase in virulence for this tissue. About the fiftieth passage death of embryos on the third or fourth day began to occur. A rather sudden increase in pathogenicity was observed around the sixty-third passage, all embryos after that stage dying on the third day after inoculation, with striking lesions of hemorrhagic encephalitis. A still further increase of virulence was evident by the seventy-fifth passage, when embryos died within 48 hours and showed multiple hemorrhages in the skin and muscles as well as in the brain.

Corresponding to the gradual development of virulence for the embryo there was a steady loss of virulence for the ferret, and experiments with

human beings indicated that the egg passage virus was almost or completely non-pathogenic when administered intranasally, but was capable of causing a rise in antibody titre in about 50 per cent of those tested. These experiments are quite recent and much more work must be done. To have at hand a means of attenuating the virulence of influenza virus for man is however, a very hopeful beginning.

Increase in virulence for the chick embryo by repeated passage, associated with a reduction in virulence for the native host but with a retention of immunizing power is illustrated also by the virus of infectious bronchitis of fowls. In a recent letter F. R. Beaudette, of the New Jersey Agricultural Experiment Station, has written me that a strain of the virus of fowl bronchitis which he has been cultivating in incubating eggs for some time " seems to have lost its ability to induce disease in fowls entirely, but the killing time for embryos has grown shorter until now it kills in from 24 to 48 hours. Moreover, inoculated chickens seem to develop an immunity to subsequent inoculation with virulent field virus. Similarly fowls tested before inoculation show no neutralizing bodies but they are demonstrable two weeks after inoculation although the chickens have shown no symptoms indicative of infection."

Not all viruses propagated in the embryo exhibit such a great loss of virulence for the usual susceptible host. A strain of vaccine virus, for example, which has been propagated in my laboratory through 250 generations in the membranes during the last seven years by G. J. Buddingh has varied little in its potency for the rabbit and man since the first ten generations several years ago, and is now almost as virulent for rabbit and human skin as the original dermovaccine from which it was derived.

5. The Culture of Viruses for Chemical and Physical Studies of Their Nature

Lush and Burnet had good results from the use of infected chick membranes as a source of antigens for complement fixation reactions with the viruses of human influenza, swine influenza and rabbit myxomatosis. These were the only viruses tested. Myers and Chapman report that membranes infected with vaccinia provide satisfactory antigens for complement fixation tests.[12]

Our own observations show that infected embryos afford a bountiful source of relatively pure virus in such infections as fowl-pox and vaccinia. The experiments of Katherine Anderson and those of J. R. Dawson, Jr., also indicate that similarly large quantities of the viruses of herpes simplex and of rabies respectively can be obtained from the infected tissues of chick embryos for chemical and physical studies, and possibly as a source of vaccines.

6. Iso- and Hetero-Grafting on the Membranes of Chick Embryos as an Indirect Means of Studying Virus Infections

As has been already stated there are some viruses which thus far have resisted attempts to cultivate them in the tissues of the chick embryo. In consideration of this failure and because of a desire to study certain problems of immunity experiments were undertaken in order to determine whether or not it would be possible to graft alien tissues onto the chorio-allantoic membrane of chick embryos after the method of Murphy.[18] In this way it might be possible to study virus infection in the tissues of their native host and thus by indirection to create experimental conditions favorable also for studies of cellular and tissue immunity.

Last year Beverly Douglas, Katherine Anderson and I succeeded in grafting human skin upon the chorio-allantois of chick-embryos.[15]

We found that the thin skin (Thiersch grafts) adhered and were nourished for as long as 10 days, which represents the longest period available on a single developing egg with the graft implanted at 10 days of incubation. Occasionally regrafts upon a second egg succeeded, thus prolonging the vitality of the graft for several days longer.

In successful experiments the epithelium of the chorio-allantois fuses with that of the graft, the collagen fibers of the chorium interlace with those of the membrane after the separation or disappearance of the ectodermal layer, and the blood vessels of the chick anastomose, or unite by intervening pools of extravasated blood, with those of the graft. This vascular communication between the two tissues is largely responsible for the nourishment of the graft by affording a plasmatic circulation. Gradually there is a revascularization of the graft by an ingrowth of blood vessels from the chick membrane. Isografts and other heterografts, namely rabbit skin, have been successfully grafted in this way.

From the standpoint of studies of infection and immunity to viruses several possibilities for useful application of this method of skin grafting are apparent.

In the first place there is afforded an opportunity to investigate the susceptibility of skin thus grafted to viruses with which so far successful infections of the chick embryo have not been demonstrated, for example, the viruses of measles, chicken-pox, herpes zoster, molluscum contagiosum and warts. If this should prove to be possible, a means would be at hand to study these viruses by indirection and possibly to adapt them to the chick embryo tissues. We have already found that human skin grafts are susceptible to infection with the viruses of smallpox, vaccinia and herpes simplex, but up to the present time we have not had adequate opportunity to study other viruses.

The method is adaptable also to studies of immunity, for the skin of immunized animals can be grafted quite as readily as that of susceptible animals of the same species.

As will be mentioned later we have already made some progress in this direction, although our investigations are still incomplete.

7. Use of the Chick Embryo for Studying Immunity

There are many problems of immunity that need new technical approaches and our experiments with chick embryos early indicated that they might advantageously be used in certain ways to investigate some phases of the immunity phenomena.

From the standpoint of natural immunity our early experiments with the virus of herpes simplex demonstrated that tissues of the chick embryo are highly susceptible to infection by this agent notwithstanding the fact that newly hatched chicks seem to be completely resistant. Here is a problem of the utmost significance—the acquiring of complete resistance from a state of high susceptibility by the processes of maturation—and an experimental animal available for its investigation. We have begun preliminary study of this phenomenon, but our progress thus far has not been sufficiently extensive to report at this time.

It is a matter of common knowledge that hosts which recover from an infection by most viruses become resistant to subsequent infection by the same virus for varying periods of time, not infrequently for life. This is an example of acquired immunity—a result of the phenomena of infection. Under such circumstances it is usually possible to demonstrate that the host has acquired certain properties differing from those present during the previously susceptible state. One of these properties is the capacity of the blood serum to prevent virus from causing infection in an otherwise susceptible host. Following certain infections whether viral or bacterial the serum possesses also the capacity to agglutinate and to dissolve the infective agent. The dissolving effect seems to be dependent upon complement, usually present in normal serum, acting in conjunction with a specific antibody.

So far as our experiments have gone it appears that the chick embryo does not possess the capacity to produce specific antibodies, in effective amount if at all, and our investigation concerning the presence of complement has shown that none can be demonstrated up to the time of hatching.

These facts present an interesting situation with reference to analyzing certain factors of immunity, because it has long been known that under certain circumstances a temporary immunity can be conferred upon a susceptible host by introducing into its body the serum or blood of a host that has recovered from the disease against which protection is desired.

We have since developed a method whereby antisera, with or without complement, can be injected directly into the blood stream of chick embryos, so that analyses can be made of the various factors concerned in the processes involved in passive immunization.

With respect to the immunity that follows a virus infection there is the very important question as to whether all the phenomena of immunity are due to change in the body fluids, i.e. humoral immunity, or that the cells of the immune host themselves possess an acquired resistance. This question is an especially pressing one in relation to virus immunity because it is now quite generally accepted that a virus must penetrate certain cells of the host in order to multiply and thus induce disease.

Katherine Anderson and I have recently undertaken a study of some of these questions in relation to immunity to fowl-pox, using especially the method of grafting skin from normal and immune chickens onto the chorio-allantoic membrane of chick embryos.

Following recovery from fowl-pox chickens become completely immune to subsequent inoculation with the virus of this disease. The tissue specifically affected by this virus is the epithelium of the skin, consequently this tissue offers an exceptionally favorable opportunity for the grafting experiment.

Skin from normal and from immune chickens was grafted together or alone upon the chorio-allantois of developing eggs after 10 or 12 days of incubation. After four days, at which time they were well established, the grafts were inoculated with fowl-pox virus. The result was that the epithelial cells from immune chickens became infected quite as readily as those from normal chickens.

In other words we have as yet found no evidence to support the view that epithelial cells acquire an intrinsic immunity as a result of fowl-pox infection. These experiments are being continued in an effort to discover the mechanism of acquired resistance, but we cannot make a more extensive report at the present time.

Summary

The success of future studies of infections caused by viruses, and the state of immunity that frequently follows, will depend very largely upon the experimental animal used. Likewise, so far as one can foresee, we must rely upon suitable hosts, whether they be living cells in tissue cultures or organized living animals and plants, for obtaining antigenic substances and vaccines to be used in attempts to improve methods of prophylaxis.

Although efforts to employ the chick embryo for these purposes are recent and the results limited, enough has already been accomplished to indicate that this method holds much promise of usefulness, and it is my opinion, based upon our own experiences during the past few years, that if it should be given a more general application to such problems as I have indicated, its use would facilitate progress in virus research.

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VISUALIZATION OF THE CHAMBERS OF THE HEART AND THE THORACIC BLOOD VESSELS IN PULMONARY HEART DISEASE; A CASE STUDY *

By GEORGE P. ROBB, M.D., and ISRAEL STEINBERG, M.D., *New York, N. Y.*

PULMONARY heart disease, or *cor pulmonale*, has long been known as a disorder which tends to develop in the course of certain chronic pulmonary diseases. Emphysema [1, 2, 3] and pulmonary fibrosis [4, 5, 6] have, perhaps, been mentioned most frequently in this connection, but other types of lung disease which cause extensive obliteration or narrowing of the smaller pulmonary blood vessels may produce it.[7] Among these are primary endarteritis obliterans of the pulmonary arteries [8, 9]; obliterative endarteritis due to metastatic carcinoma [10, 11] and *Schistosomiasis mansoni* [12]; chronic pulmonary embolism [13, 14]; and the pulmonary fibrosis and emphysema produced by spinal and thoracic deformity.[15, 16, 17] The principal pathological changes occurring in the heart consist of dilatation and hypertrophy of the right ventricle,[18, 19] particularly the outflow tract [20, 21] although in advanced cases the inflow tract also is involved, dilatation of the pulmonary artery and its larger divisions and, eventually, with the onset of heart failure, enlargement of the right atrium. The left ventricular hypertrophy so frequently associated with this condition is probably due to systemic hypertension or other independent causes of heart disease,[3] although myocardial anoxemia has been cited as an etiological factor.[2] It is generally agreed,[3, 19, 22] although not unanimously,[2] that the enlargement of the right ventricle and the pulmonary artery is caused by the pulmonary hypertension which develops as a result of the increased resistance to blood flow through the pulmonary circulation in chronic lung disease.

Although the pathological changes in pulmonary heart disease are well defined, the diagnosis of this disorder presents unusual difficulty, for there are no pathognomonic symptoms or physical signs. The dyspnea, cough, cyanosis, and weakness so frequently encountered and ascribed to early cardiac failure are due entirely to the underlying pulmonary disease.[19] Enlargement of the right ventricle cannot be detected accurately by percussion, and the systolic murmur frequently heard at the pulmonic area and the accentuation of the pulmonic second sound are not distinctive. Right axis deviation of the electrocardiogram is not a constant or dependable

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guide [3] in this disease. Measurement of the circulation time has no diagnostic value,[23] and the venous pressure remains normal [24] except in the presence of right ventricular failure, although an elevation of the venous pressure in uncomplicated emphysema has been reported.[1] There is evidence that the saline infusion test of myocardial efficiency may permit the recognition of this disorder [24] but experience is yet too limited to warrant any conclusion. In the absence of heart failure, *cor pulmonale* is symptomless and unobtrusive; and, when heart failure does supervene, the evidence must be looked for in the engorgement of the peripheral veins, enlargement of the liver, ascites, and dependent edema, and not in disturbance of the pulmonary circulation. Since other clinical methods have consistently failed in the detection of this type of heart disease, it has been necessary to employ roentgenology for its diagnosis.

The value of roentgenologic examination of the heart has been appreciated almost since Roentgen's discovery of the x-ray in 1895. Since then the characteristic appearance of the cardiac silhouette in the various types of heart disease has been worked out and is now generally known. Dietlen [25] was probably the first to investigate the heart in emphysema. He reported his orthodiagraphic studies in this condition as well as in mitral and aortic valvular disease in 1908, and described the rounded shape, the apparent smallness and the low central position of the heart in the chest which he ascribed to the low diaphragm. Groedel [26] in 1912 commented upon the clear visibility of the apex of the heart and the inferior vena cava in this condition and questioned whether the apparent smallness of the heart was due to an actual decrease in size or to its central position and elongation. Both these observers recognized that independent heart disease frequently modified the cardiac outline in emphysema. Three years later, Staehlin [27] confirmed these observations and called attention to the poor definition of the aortic arch and to the prominence of the middle curve of the left border of the heart in the frontal view which appeared to be pulled up. In 1916, Lutembacher [28] described the striking prominence of the pulmonary arc in five patients with great enlargement of the right ventricle. In his book in 1924, Dietlen [29] summarized the roentgenographic evidence of right ventricular hypertrophy in emphysema. He noted enlargement of the heart transversely to the right, protrusion of the lower right edge of the heart which was separated from the right auricle above by a notch, prominence of the pulmonary arc with forceful pulsation there and at the lower right cardiac border, and lengthening of the right ventricular curve in side view. Vaquez and Bordet [30] described the bulb-shaped heart due to transverse cardiac enlargement and the prominence of the larger pulmonary vessels. They also observed the " sabot " heart in emphysema. Assman [31] emphasized the enlargement of the pulmonary curve and the prominence and pulsation of the hilar blood vessels. Finally Clerc and Mourrut [32] reported a case of *cor pulmonale* and completed the roentgenographic picture of this condition by emphasizing the enlargement of the hilar blood vessels and their

tortuous descending branches on each side which they likened to a "moustache."

In their comprehensive study of the heart in emphysema, Parkinson and Hoyle [3] reviewed the literature on this subject and reported in detail their clinical and roentgenographic observations in 80 patients with high grade emphysema, 58 per cent of whom had pulmonary heart disease. They noted the frequency with which the heart was affected by other cardiovascular disease, notably hypertension, although it frequently escaped the involvement due to emphysema. They observed roentgenographic changes in the stem and the branches of the pulmonary artery in 58 per cent of their series. These consisted of enlargement and increased density of the right and left branches of the pulmonary artery and their branches in the hilar and surrounding area. Undue prominence of the pulmonary arc was observed in 35 patients (44 per cent) but not the excessive pulsation or the striking degree of enlargement characteristic of mitral stenosis and congenital heart disease. These changes in the main pulmonary artery and the primary branches could generally be demonstrated more clearly in the oblique positions. Enlargement of the "pulmonary conus," they believed, was the most frequent indication of actual cardiac enlargement in emphysema, although it was detectable less often than the pulmonary arterial changes. It was rarely demonstrable in the frontal view, requiring the right oblique projection for its detection. Involvement of the body of the right ventricle offered unusual difficulty in recognition, for it could rarely be shown in the frontal view, and only in a small proportion of cases in the left oblique position which is the projection of choice. Enlargement of the right atrium was noted infrequently, and that of the left atrium only once—in a patient with auricular fibrillation. Left ventricular enlargement usually due to hypertension was present in 30 per cent of their cases.

These authors tried to apply the conventional methods of cardiac measurement to the diagnosis of pulmonary heart disease but concluded that mere inspection of the heart shadow by an experienced observer was more reliable than any system of measurement. Measurements of the transverse diameter, the cardio-thoracic ratio, and the transverse diameter in the left oblique position by Fray's method, were unsatisfactory as indices of cardiac enlargement because of the barrel shape of the chest and the long narrow form of the heart. Measurements of the pulmonary conus and artery by the methods of Vaquez and Bordet and Abreu likewise were found to be unreliable guides to enlargement of these structures. Commenting upon the unsatisfactory results obtained with cardiac measurement in this disease, Parkinson and Hoyle stated: "There would be advantages in a reliable scheme for measuring enlargement of individual chambers of the heart and of the great vessels. But we are convinced that this is not yet feasible except when such enlargement is of a very gross kind." Accurate measurement of the chambers of the heart, the pulmonary circulation and the great

vessels has, however, become a possibility since the publication of their paper in January, 1937.

We have recently developed a practical method for visualizing the heart and the thoracic blood vessels.[33, 34] It consists of the rapid intravenous injection of a concentrated (70 per cent) solution of diodrast into a large vein of the arm and the taking of roentgenograms at the moment of opacification of the structures to be visualized. In normal individuals the superior vena cava and the right atrium are filled in one to one and a half seconds after the beginning of injection, the right ventricle and the pulmonary artery and its branches in three seconds, and the left atrium, the left ventricle and the aorta in from six to ten seconds. In the right heart, the following structures have been identified: The superior vena cava and its tributaries; the right atrial and ventricular cavities and walls; the auricula; the tricuspid valve; the trabeculae; the ventricular septum; the pulmonic valve, and the pulmonary artery with its sinuses and subdivisions. The following components of the left heart have been seen and studied: The pulmonary veins; the left atrial and ventricular walls and cavities; the auricula; the cusps of the aortic valve, and the entire thoracic aorta including the sinuses and the innominate, the left common carotid, and the left subclavian branches from the arch.[34, 35] Characteristic changes in heart [36] and lung disease [37, 38] have been reported.

The purpose of this paper is to demonstrate the value of detailed visualization of the heart and the thoracic vessels in a patient with pulmonary heart disease and to indicate its importance in the recognition of this not uncommon but frequently overlooked condition.

Case Report

H. G., an unemployed, 57 year old, white American laborer was admitted on March 23, 1938, because of an attack of " faintness " which had occurred three hours earlier. Because of uncoöperation and defective memory, an adequate history was unobtainable. For many years he had had cough and the expectoration of yellow mucoid sputum which, in his estimation, amounted to six to eight ounces daily. He denied having had hemoptysis or chest pain, but had experienced moderate dyspnea upon climbing two flights of stairs. For the past three years he had been unemployed and homeless and had eaten irregularly, having had only soups and stews with an occasional sandwich. He admitted the excessive use of alcohol in the past with an average ingestion of a quart of whisky a day until the past year when it, too, had become difficult to obtain. He had always considered himself well and denied any previous illnesses; although he finally recalled that many years ago he went to a chest clinic because he thought he might have pulmonary tuberculosis. Apparently he was reassured, for he had no further occasion to seek medical care. The attack of " faintness," which was the first he had ever experienced, occurred on the street, and a passerby summoned an ambulance. On arrival at the hospital, the patient denied convulsive seizures, precordial pain, and any symptom except the " faintness " and the cough and expectoration.

Examination on entry showed the patient to be poorly developed and nourished, and he appeared to be chronically ill. His temperature was 102 degrees. He was slightly dyspneic while lying flat in bed but not orthopneic, for the dyspnea was not

relieved by elevation of the bed. Both pupils were irregular and reacted sluggishly to light. Ophthalmoscopic examination revealed only a moderate degree of tortuosity of the vessels and no hemorrhages or exudates. The tongue and mouth were essentially normal, but examination of the throat was not possible because the patient refused it. The thorax was barrel shaped with flaring of the costal margins, and the

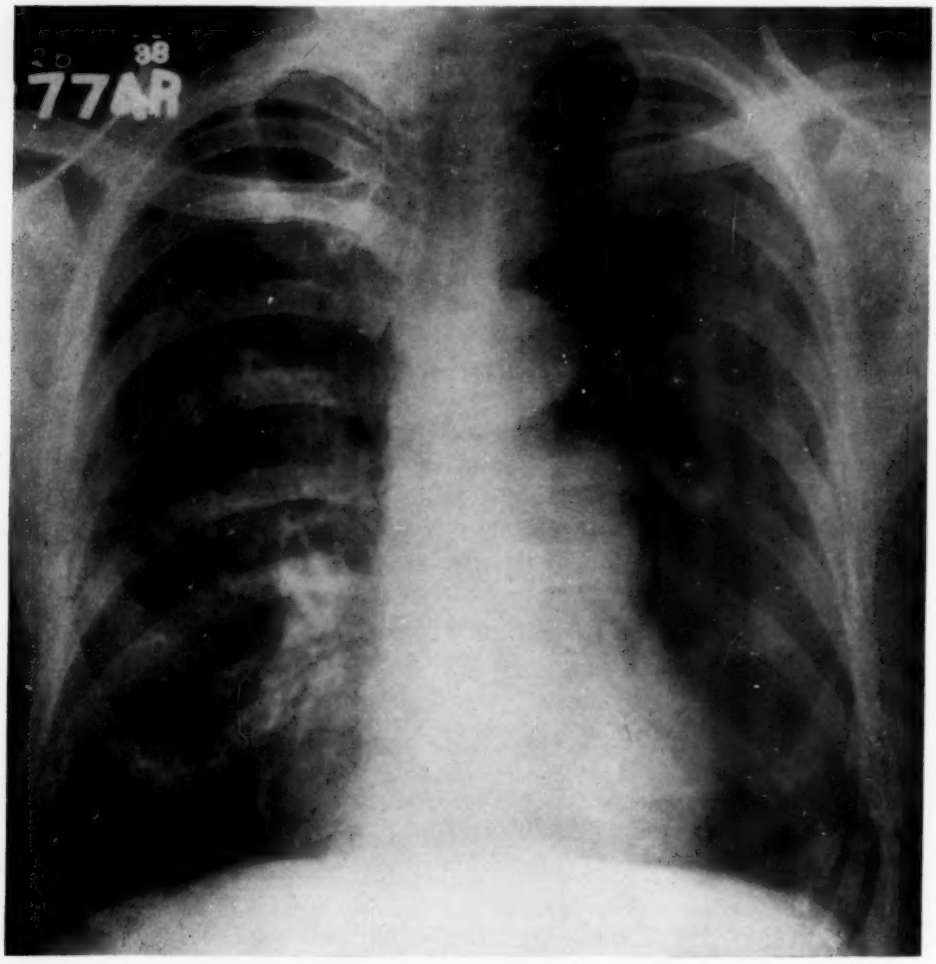

FIG. 1. *Conventional Roentgenogram—Frontal View.*

Note central position of heart, prominence of right lower border and pulmonary arc and calcification of aortic knob. Hilar blood vessels and right inferior branches unusually prominent. Decreased vascularity of mid and peripheral zones, widened interspaces, and large emphysematous bulla at right base characteristic of emphysema. Note cavity with fluid level in lung near right hilum.

chest moved *en masse*. There was hyperresonance to percussion and the breath sounds were diminished throughout. Expiration was prolonged with expiratory wheezing. The point of maximum impulse of the heart was in the fifth interspace, 8.5 cm. from the midsternal line and within the midclavicular line. The heart sounds were distant; the aortic second sound was moderately accentuated, ringing in character, and greater

than the pulmonic second sound which, however, seemed louder than normal. There was a faint systolic murmur at the aortic area and either a split first sound or soft systolic murmur at the apex. No pulmonic murmur could be heard. The rhythm was regular with a ventricular rate of 100. The blood pressure was systolic, 100, and diastolic, 60. The abdominal examination was entirely negative; the liver was palpable at the costal margin only on deep inspiration; and there was no ascites. Except for a moderate degree of cyanosis of the nail beds and slight to moderate sclerosis of the radial and brachial arteries, the extremities were not remarkable; there was no venous engorgement, edema, or clubbing. Examination of the neuromuscular systems revealed no abnormality except for tenderness of the calf muscles.

Laboratory Examinations: The urine was repeatedly normal. The erythrocyte count varied between 3.09 and 3.9 millions per cu. mm. and the hemoglobin from 10.2 to 11.3 grams per 100 cu. cm. The morphology of the red blood cells was normal. The leukocyte count on admission was 9,050 with the following distribution of cells: polymorphonuclears, 58 per cent, lymphocytes, 36 per cent, and monocytes, 2 per cent. The Wassermann test was negative, and the chemical examination of the blood showed no abnormality; the non-protein nitrogen was 33 and the blood sugar 120 mg. per cent. The sputum examination made on admission was negative for the tubercle bacillus, and the sputum typing performed on the same day showed unclassified pneumococci. The blood culture was sterile. The vital capacity was 1.9 liters, equivalent to 1.09 liters per square meter of body surface, which represented a decrease of 58 per cent below the average normal.

The conventional six-foot roentgenograms to be described later showed localized and generalized emphysema, calcified tubercles in the right upper lung field, and a cavity of unknown etiology in the lower part of the right upper lobe near the hilum. The heart was triangular in shape, enlarged transversely to the right with striking prominence of the pulmonary arc. The aortic knob was prominent and showed a small area of calcification. An attempt to fill the pulmonary cavity with iodized oil was unsuccessful, but the right middle and lower lobe bronchi were outlined and showed the slight dilatation of the terminal bronchioles frequently found in emphysema. Esophagrams taken in the frontal, the lateral, and both oblique positions were entirely normal.

Conventional electrocardiograms showed regular sinus rhythm, no deviation of the electrical axis, and slurring of the QRS in Leads II and III. The T-wave was low in Lead I and diphasic in II and III. Precordial electrocardiograms taken from points V_1 to V_5 were normal except for inversion of the T-wave at V_3.

Course: On entry the patient appeared acutely as well as chronically ill. His temperature varied between 100 and 102 degrees, reaching a maximum of 103 degrees on the seventh day. Subsequently the fever subsided and his temperature remained normal until his discharge on May 23, 1938, two months after admission. While on the ward his sputum was noted to be mucopurulent, and postural drainage was attempted but was unsuccessful because the patient would not coöperate. On routine hospital diet, the evidence of peripheral neuritis disappeared; and after ten days of hospital care, he felt completely well and became ambulatory. Since discharge he has been seen at frequent intervals in the Outpatient Clinic and no change has been observed in the status of either the heart or the lung disease.

Clinical Diagnoses:

I. *General:*

Peripheral neuritis due to avitaminosis B_1.

II. *Pulmonary:*

Chronic pulmonary tuberculosis, IA, healed. (Right apex.) Chronic bronchitis. Pulmonary fibrosis. Bullous and generalized emphysema. Pulmonary cavity of unknown etiology (lower part of right upper lobe).

III. *Cardiac:*

(*a*) (etiologic) Pulmonary fibrosis, emphysema, and arteriosclerosis.

(*b*) (pathologic) Right ventricular hypertrophy, dilatation of the pulmonary artery, and dilatation and atherosclerosis of the aorta. Coronary sclerosis (probable).

(*c*) (physiologic) Regular sinus rhythm.

(*d*) (functional) IIA (slight diminution of cardiac reserve).

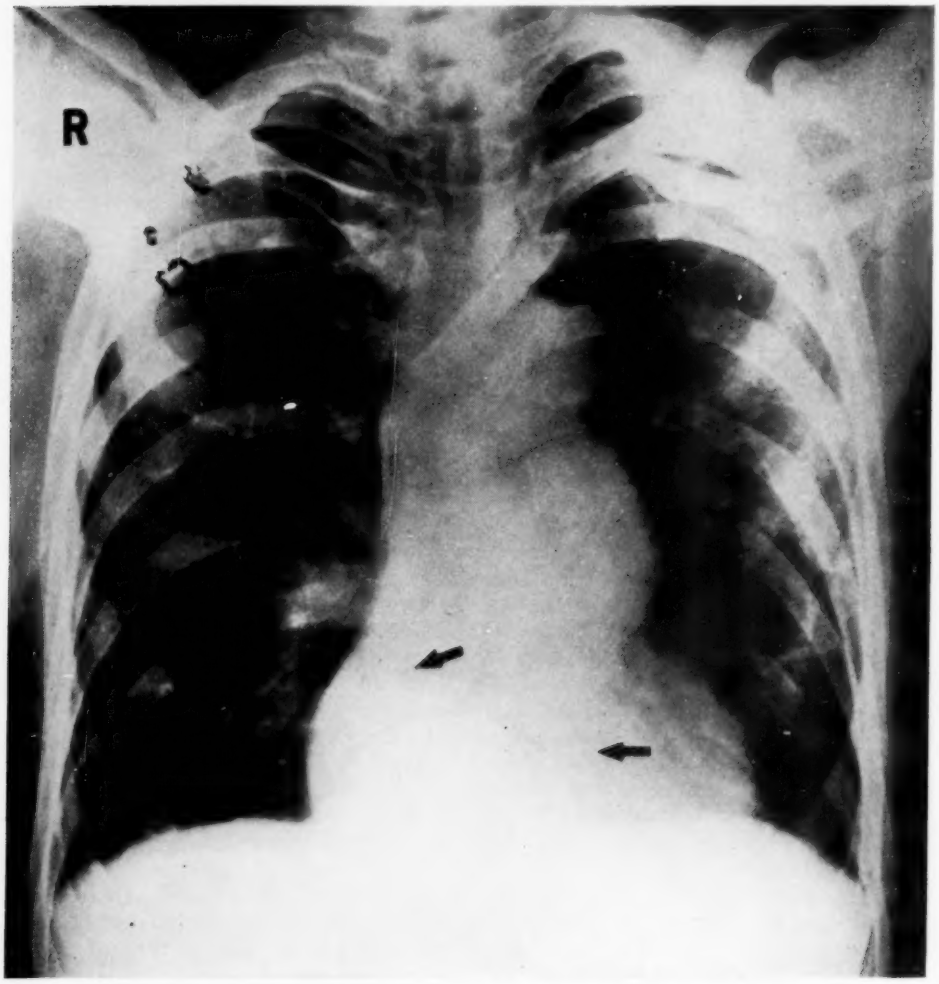

FIG. 2. *Contrast Roentgenogram—Frontal View* 4½ seconds after beginning of injection. Superior vena cava, left innominate vein and its tributaries opaque. Right atrium, right ventricle, and pulmonary artery well filled. Right atrial and pulmonary arterial walls well defined, 2 mm. in thickness. Lower arrow against ventricular septum, upper arrow indicates junction of superior vena cava and inner border of right atrium.

ROENTGENOLOGIC STUDIES:

1. *Roentgenoscopic Observations.*

The diaphragm was low and its excursion slight. The lung fields were well illuminated especially at the right base where there was a circumscribed bulla. At the

right hilar area there was a small cavity with a fluid level which shifted with change of position and was localized at the right mid lung field. The heart in all views showed normal pulsations, those on the left side being greater than those on the right. The pulmonary artery appeared dilated and the hilar vessels were larger and denser than normal while those to the outer zone were decreased in number and size. There was no "hilar dance" and the aortic pulsations were normal. The optimal angle for the right anterior oblique projection proved to be 35° and that for the left oblique view 40°.

2. Conventional Teleroentgenograms.

In the frontal view (figure 1), the position of the diaphragm was low and the ribs appeared more horizontal than normal with widened interspaces. The large emphy-

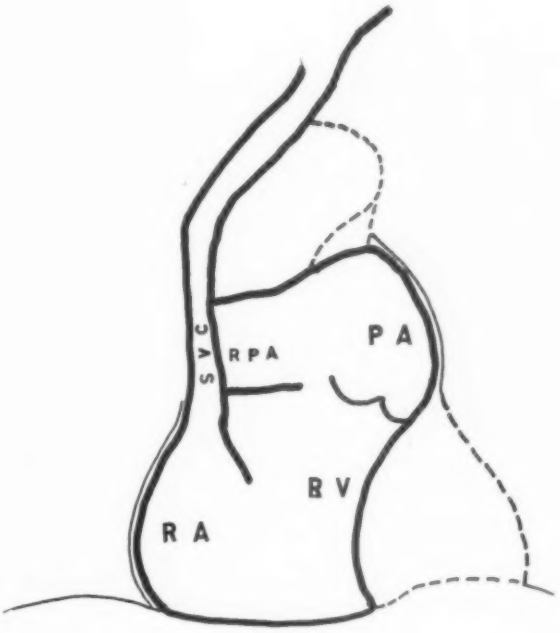

FIG. 2A. *Tracing.*

S. V. C. = superior vena cava; R. A. = right atrium; R. V. = right ventricle; P. A. = pulmonary artery; R. P. A. = right pulmonary artery. Note right and left cusps of pulmonary valve and atrial and pulmonary arterial walls.

sematous bulla on the oblique and the lateral views (figures 5, 8, 11) appeared to have a fibrous wall. Elsewhere the lung fields showed interstitial fibrosis. The right apex and the first interspace contained a few calcified tubercles (figure 1). Adjacent to the right hilum was a small cavity with a fluid level. On lateral view (figure 11), this was in the mid lung field and, subsequently, by bronchographic examination, was shown to be in the lower part of the upper lobe. The postero-anterior diameter was moderately increased.

The heart on frontal view (figure 1) was roughly triangular in shape and appeared to be more centrally placed than normally. The lowest curve of the right cardiac border was unusually prominent and the pulmonary arc was conspicuously enlarged, appearing as a prominent bulge between the aortic and the left ventricular contours. The left ventricle appeared to be normal but the aortic arch was more

prominent than usual and contained a calcified plaque. The right innominate vein and the superior vena cava were visible lying to the right of the aorta.

The right anterior oblique projection (figure 5, rotation 40°) showed conspicuous enlargement of the pulmonary artery, elongation of the heart, and dilatation and

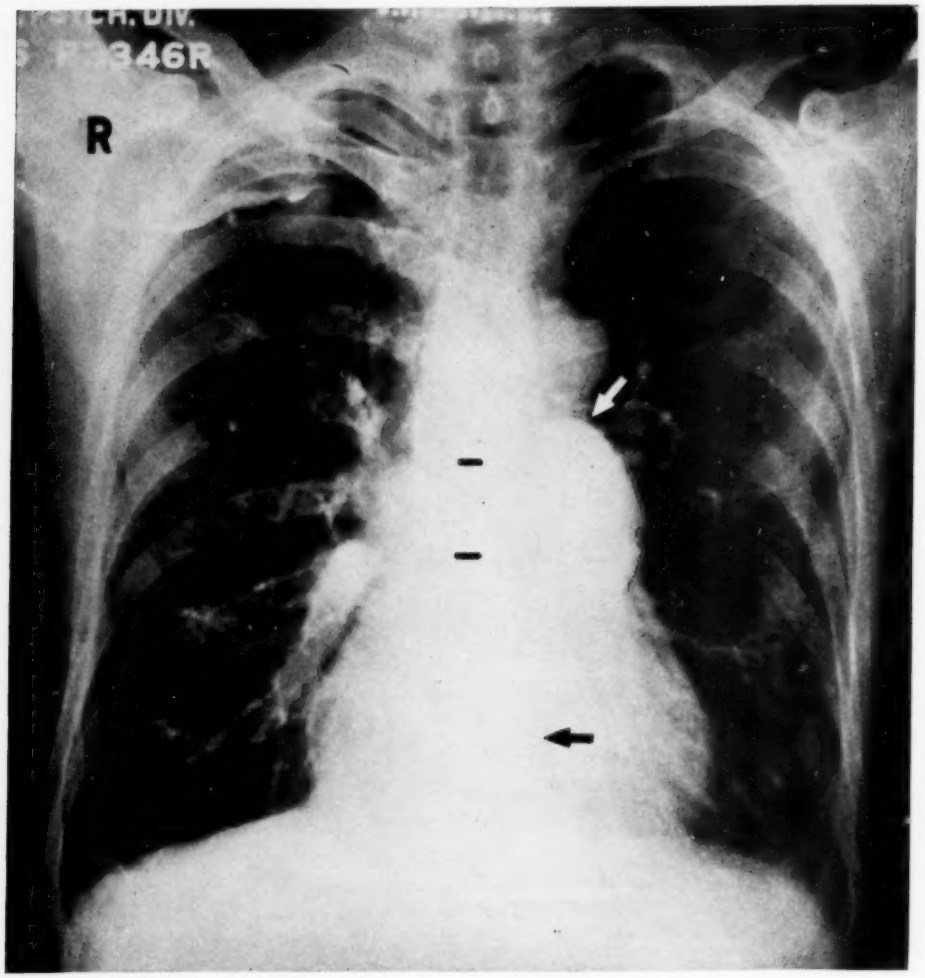

FIG. 3. *Contrast Roentgenogram—Frontal View* at 6 seconds.

Right atrium no longer opaque. Ventricular septum, left border of pulmonary artery, receding left branch and right main trunk clearly defined. Right border of ventricle and conus arteriosus indistinct. Note enlargement of the pulmonary artery and its branches as far as fourth subdivisions and decreased vascularity in mid and outer zones giving the appearance characteristic of emphysema. Black arrow denotes ventricular septum; white arrow arching and receding left pulmonary artery; parallel lines embrace right pulmonary artery.

increased density of the thoracic aorta. The retrocardiac space was clear and the esophagram, as previously noted, was of normal contour.

The left anterior oblique position (figure 8, rotation 40°) showed an unusual prominence of the lower half of the right contour, but there was no angulation of

this side. The left border was normal in shape and cleared the spine at this rotation. The receding right branch of the pulmonary artery, which was seen as the rounded density near the ascending aorta, was distinctly enlarged, as was the left branch which crossed the "aortic window" in lateral view. The aortic outline was indistinct but the arch appeared to be widened; no calcification was visible in this view.

In the lateral position (figure 11) the heart appeared to be enlarged transversely, as were the pulmonary artery and the aorta.

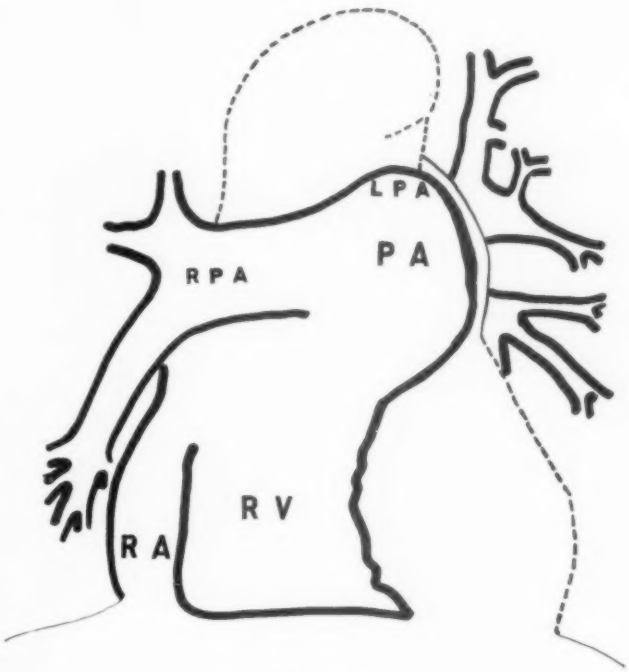

FIG. 3A. *Tracing.*
R. A. = right atrium; R. V. = right ventricle; P. A. = pulmonary artery; L. P. A. = left pulmonary artery; R. P. A. = right pulmonary artery.

3. *Contrast Teleoroentgenograms.*

I. *Frontal View:*

FIGURES 2 AND 2A MADE 4½ SECONDS AFTER THE BEGINNING OF INJECTION. The left innominate vein with its tributaries, the subclavian and basilic veins, the superior vena cava, the right atrium, the right ventricle, and the pulmonary artery were opaque. The innominate vein measuring 1.2 cm. in diameter crossed the spine to join the superior vena cava which could be followed to the right atrium. At this point, the superior vena cava measured 1.4 cm. in diameter. The right atrial wall was clearly outlined and was 2 mm. in thickness. The ventricular septum was displaced to the left, lying 9.2 cm. from the right border of the heart. Only the left border of the conus arteriosus and the pulmonary artery were visible, but two cusps of the pulmonary valve were identified. The pulmonary artery formed the prominent pulmonary arc, and its wall measured 2 mm. in thickness.

IN FIGURES 3 AND 3A, TAKEN 1½ SECONDS LATER, the right ventricle, the pulmonary artery and both main branches were visible, but the right atrium was no longer opaque.

The right ventricle formed a vertical band of density 5.5 cm. wide which rested upon the diaphragm below and passed upward and to the left to end as the conus arteriosus. The left branch of the pulmonary artery could be seen only as an upward extension of the pulmonary arterial density noted in the previous film. The right pulmonary

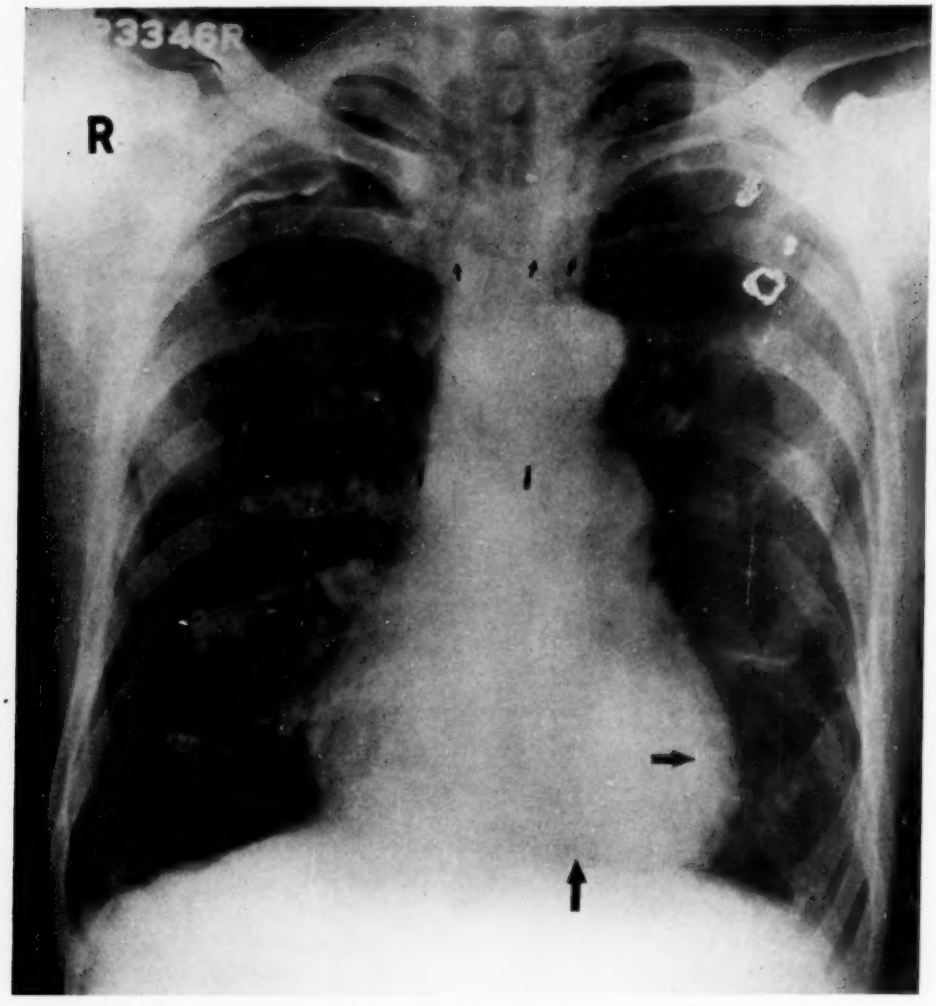

FIG. 4. *Contrast Roentgenogram—Frontal View* at 12 seconds.

Left ventricular cavity, ascending and transverse portions of aorta, innominate, left common carotid, and subclavian arteries well outlined. Large vertical arrow points directly to ventricular septum which curves upwards and to right. Left ventricular cavity lies above and to left of arrow; ventricular wall well defined and inner border indicated by horizontal arrow. Parallel lines enclose ascending aorta. Note thickness of wall at aortic knob. Small arrows upon branches at arch.

arterial branch was outlined distinctly as it crossed to the right and divided at the hilum. Its diameter was 3.4 cm. and that of the descending branch 1.8 cm. at its origin and 1.4 cm. at the level used by Assman.[31] The pulmonary arterial branches in the inner and middle zones seemed thicker, denser, and stiffer than normal, while there was decreased vascularity towards the periphery.

FIGURES 4 AND 4A, MADE AT 12 SECONDS. The left atrium, the left ventricle, and the ascending and transverse portions of the aortic arch were well filled. The left ventricular cavity appeared to be somewhat enlarged. There were two curved lines along the left border of the heart. The irregular inner one, which was continuous with the left ventricular cavity, appeared to represent the inner border of the ventricular wall. It lay 1.4 cm. from the outside of the heart; whereas the more distinct middle curve in the apical region measured 7 mm. from the outer border. The left aortic cusp and the inner border of the aorta were faintly outlined. The diameter of the ascending aorta measured 3.4 cm. and the aortic wall 3 mm.

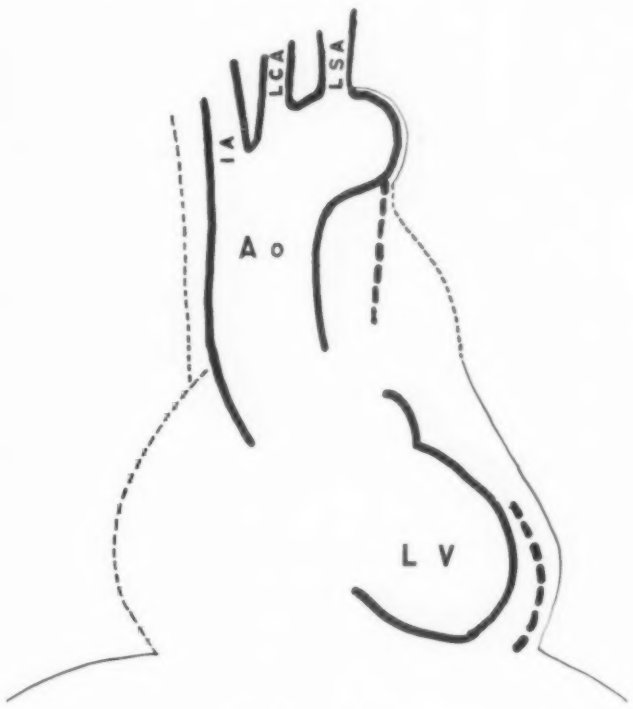

FIG. 4A. *Tracing.*

L. V. = left ventricle; Ao. = aorta; I. A. = innominate artery; L. C. A. = left common carotid; L. S. A. = left subclavian artery. Note dotted line at apex dividing ventricular wall, also parallel course of innominate vein and artery and that superior vena cava lies well beyond aorta.

II. *Right Anterior Oblique Projection* (Rotation 35°):

FIGURES 6 AND 6A, MADE AT 5½ SECONDS. The superior vena cava, the right atrium, the inflow and outflow tracts of the right ventricle, the left posterior cusp of the pulmonary valve, the pulmonary artery and its right and left branches were opacified. The right atrium lay immediately behind and slightly above the right ventricle and measured 5.8 cm. in the vertical diameter and 3.4 cm. in the horizontal. The coronary sulcus indicating the site of the tricuspid valve was clearly seen. The inflow portion of the right ventricle, which extended from the coronary sulcus to the apex of the right ventricle, measured 8.5 cm. in length and 5.5 cm. in depth, while the outflow portion taken from the apex of right ventricle to the pulmonary cusps was 8.7 cm. Trabeculations and narrowing of the cavity anteriorly produced ir-

regularity and the lessened density near the apex. The conus was well outlined and appeared to be widened, having a diameter of 3.8 cm. The pulmonary artery was strikingly enlarged, measuring 4.0 cm. in diameter and 4.5 cm. in length; and the right branch was dilated, having a diameter of 3.2 cm. at the bifurcation of the main trunk. Its subdivisions also were enlarged, the inferior trunk being 1.9 cm. in diameter at its origin.

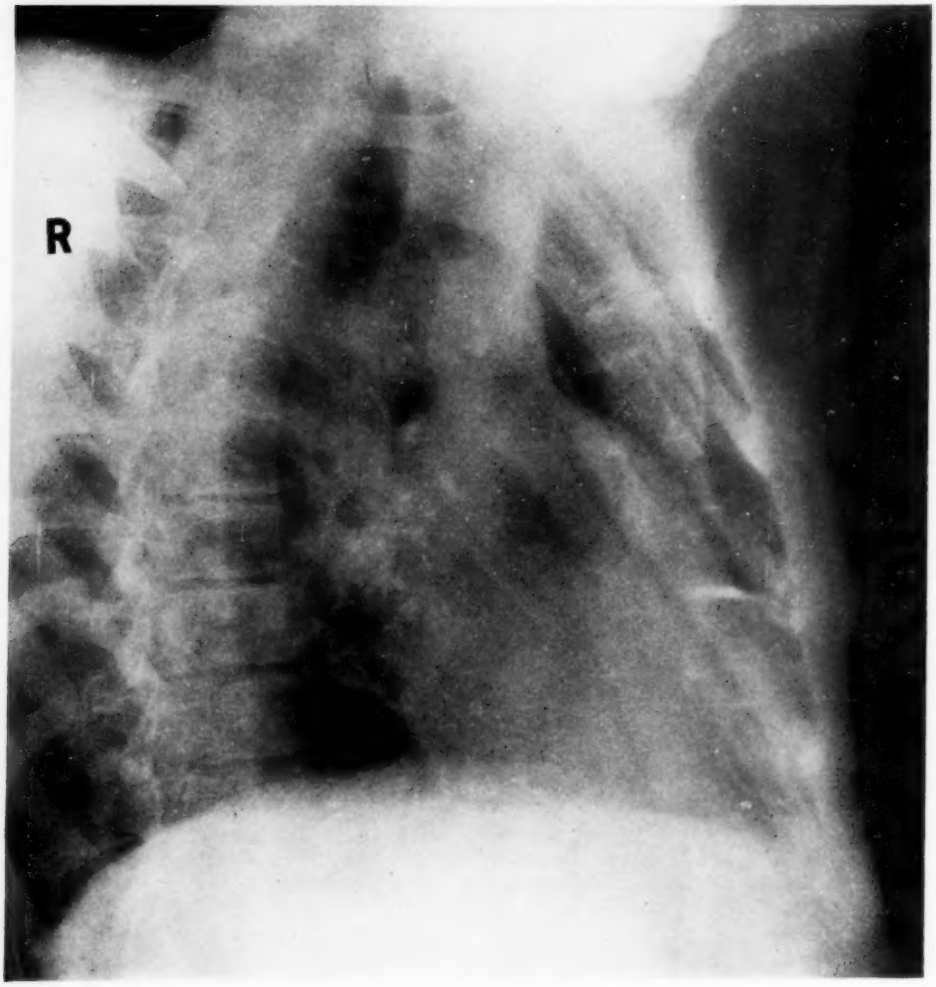

FIG. 5. *Conventional Roentgenogram—Right Anterior Oblique Projection.*
Note increased horizontal diameter of heart and angular prominence of pulmonary curve. The aorta is larger and denser than normal.

FIGURES 7 AND 7A, MADE AT 11 SECONDS. The left atrium, the coronary sulcus, the left ventricle, the left aortic cusp, the aortic sinuses, and the aorta with its branches from the arch were well visualized. The left atrium measured 5.0 cm. in vertical diameter and 3.0 cm. horizontally. The left ventricle from the coronary sulcus to the apex measured 10.5 cm. The internal diameter of the aorta immediately above the

sinuses was 3.3 cm. and the total diameter 4.1 cm. The aortic wall was well defined and measured 4 mm. in thickness.

III. *Left Anterior Oblique Projection* (Rotation 40°):

FIGURES 9 AND 9A, MADE AT 4.5 SECONDS. The right atrium was outlined although partly obscured by the overlying right ventricle. The inflow tract was seen as an indistinct rounded shadow near the diaphragm extending from the right border to the septum and measuring 6.2 cm. transversely. Its outer wall was 5 mm. in thickness. The outflow tract appeared as a vertical band of density extending from the diaphragm to the pulmonary orifice and measured 7.8 cm. in length and 4 cm. in diameter at the conus. The pulmonic cusps were faintly outlined. As in the right oblique view the pulmonary artery appeared conspicuously dilated having a diameter of 4.5 cm.; its length could not be determined accurately. The diameter of the left branch at the bifurcation was 4.4 cm.

FIGURES 10 AND 10A, MADE AT 11 SECONDS. The left atrium, the left ventricle, and the entire thoracic aorta, including the sinuses and the branches from the arch, were visualized. The left atrium formed a rounded density lying behind the upper left quadrant of the heart into which the superior pulmonary vein emptied. The left ventricle forming the remainder of the left cardiac shadow lay in front of the atrium overlapping its anterior border; at this point there was an elliptical shadow. The ventricular septum formed the convex anterior border of the left ventricular cavity, midway between the right and the left borders of the heart. The thickness of the left ventricular wall could not be estimated. Two cusps of the aortic valve were visible midway between the right and left borders of the heart, and above them the entire thoracic aorta which showed a moderate degree of generalized enlargement and "unfolding." The diameter of the ascending aorta was 4 cm., the transverse aorta 3.5 cm., the descending portion 3.4 cm., and the entire length of this vessel from the aortic valve to the diaphragm was 30.5 cm.

IV. *Left Lateral Projection:*

FIGURES 12 AND 12A, MADE AT 4½ SECONDS. The faintly outlined right innominate vein and superior vena cava passed downward midway between the spine and the sternum to enter the right atrium. The right atrium, the right ventricle with the pulmonic cusps, and the pulmonary artery with its sinuses and both major branches were opaque. The right atrium appeared as a round shadow lying behind the center of the cardiac mass and covered anteriorly by the inflow tract of the right ventricle which extended to the cardiac apex. The anterior border of the heart was formed exclusively by the outflow tract of the right ventricle, whose wall measured 5 mm. in thickness. The posterior border of the outflow tract except at the conus arteriosus was not visualized. As in the other views, the pulmonary artery was strikingly enlarged, measuring 4.1 cm. in diameter immediately above the sinuses and 4.4 cm. in length. With its right and left branches, the pulmonary artery formed the letter Y.

FIGURES 13 AND 13A, AT 11 SECONDS. The left atrium, the left ventricle, and the ventricular wall were faintly but definitely outlined, while the aorta was clearly visualized. The left ventricular wall measured 14 mm. and the diameter of the aorta was the same as that observed in the oblique positions. The left atrium lay posteriorly and superiorly near the spine, and anterior to it was the left ventricle, overlying it in part and separated from it by the oval density observed in figure 10. Two aortic cusps, with the corresponding sinuses, were well defined. As in the left oblique view the aorta appeared moderately dilated and the arch widened.

Discussion

This case study illustrates the value of detailed visualization of the heart and the thoracic blood vessels in the diagnosis of pulmonary heart disease. Visualization in this instance did not contribute to the recognition of the

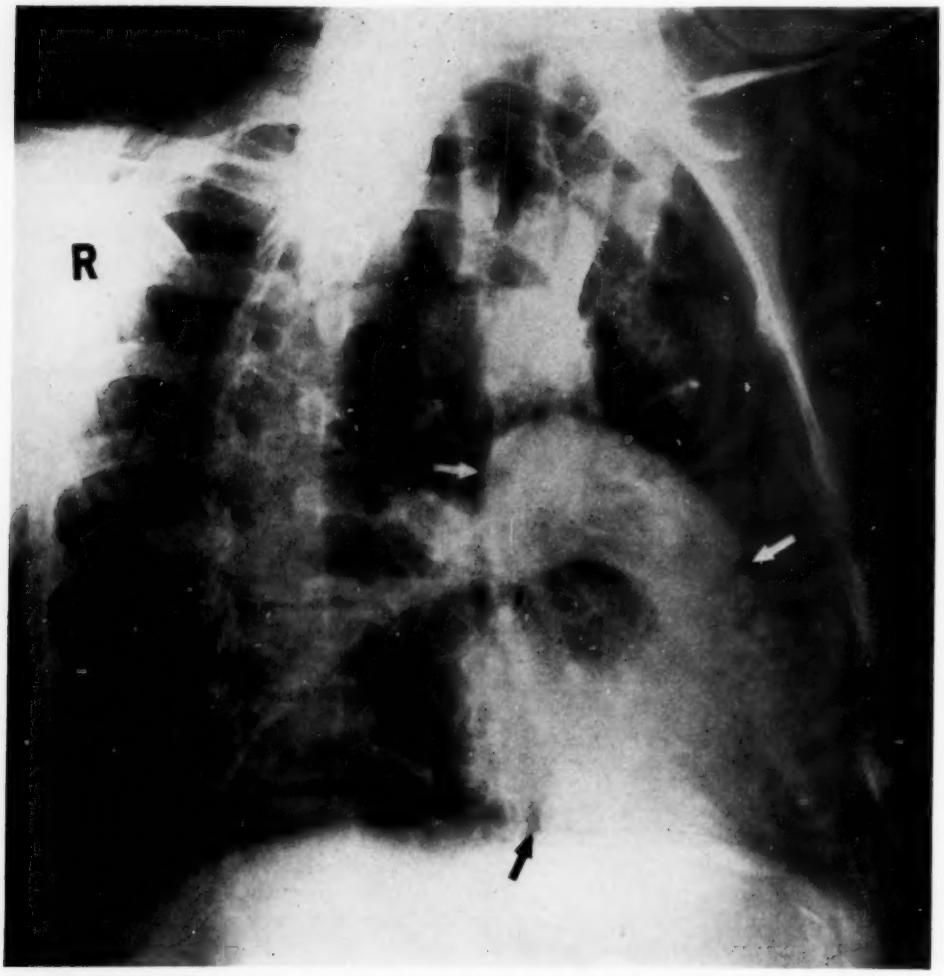

Fig. 6. *Contrast Roentgenogram—Right Anterior Oblique Position* at 11 seconds.
Left atrium, left ventricle, and ascending and transverse aorta outlined. Black arrow points to coronary sulcus; white arrow lies on left ventricular wall and indicates cavity. Small arrow lies in aorta and points downward into left cusp. Note aortic wall thickness on both sides of ascending aorta.

heart disease, which was obvious from the conventional roentgenograms. It did, however, provide a wealth of exact information regarding the structural and the functional state of the chambers of the heart, the great vessels, and the pulmonary circulation, which permitted accurate localization of the disease and appraisal of its degree.

The absence of pathognomonic symptoms and signs in pulmonary heart disease and the importance of roentgenographic examination in its diagnosis are well demonstrated by this study. Although the history of chronic bronchitis and the presence of pulmonary fibrosis and emphysema implied some degree of disease of the pulmonary artery and the right ventricle [2, 3, 6] physical examination gave no definite evidence of it. The heart was not enlarged to percussion and palpation, and there were no abnormal pulsations or murmurs which could be related to the right ventricle or the pulmonary artery. While there was some accentuation of the second sound at

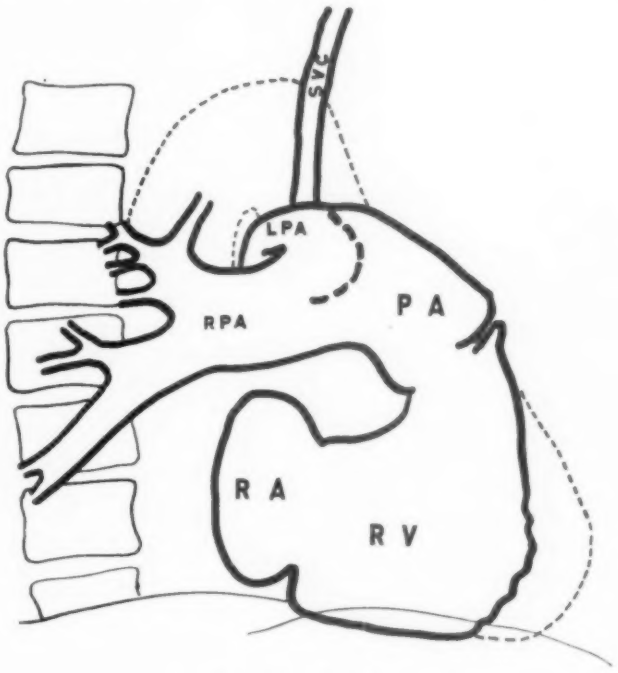

FIG. 6A. *Tracing.*

S. V. C. = superior vena cava; R. A. = right atrium; R. V. = right ventricle; P. A. = pulmonary artery; L. P. A. = left pulmonary artery; R. P. A. = right pulmonary artery.

Note bifurcation of pulmonary artery and upward arching of left branch.

the pulmonic area, it might have been due to transmission from the aortic area as well as to pulmonary hypertension and arteriosclerosis. Even the cyanosis could not rationally be ascribed to right ventricular disease and failure in the absence of venous engorgement, dependent edema, and hepatic enlargement. The vital capacity was strikingly reduced but, like the cyanosis, was undoubtedly a result of the chronic pulmonary disorder and unrelated to either right or left sided heart disease. The electrocardiogram, likewise, gave no assistance in the detection of pulmonary heart disease since there was no deviation to the right of the electrical axis or other evi-

dence of selective involvement of the right ventricle. The circulation times to the lungs and the carotid sinus, which were determined before visualization by our modification of the ether and the cyanide methods,[33, 34] showed a

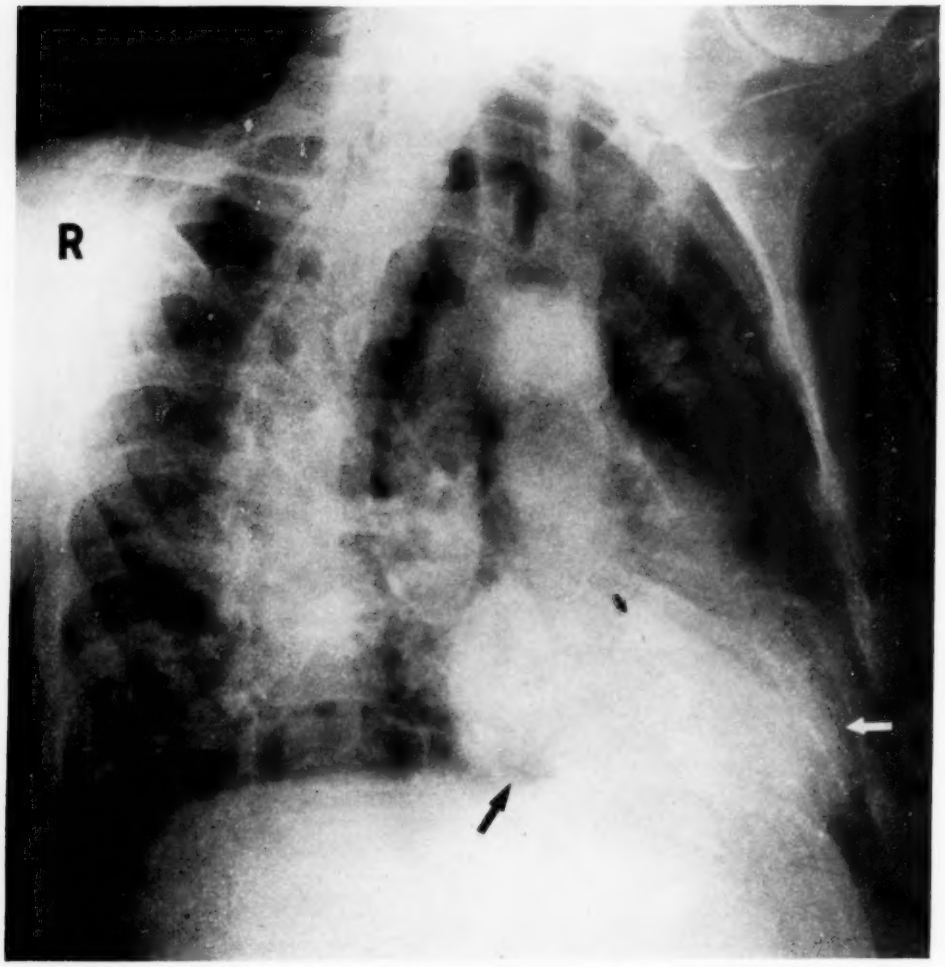

FIG. 7. *Contrast Roentgenogram—Right Anterior Oblique Projection* at 5.5 seconds.

Superior vena cava, right atrium, inflow and outflow tracts of right ventricle, pulmonary artery and its right and left main divisions opacified. Black arrow points to coronary sulcus indicating location of tricuspid valve. Inflow tract of right ventricle extends horizontally to apex and outflow tract vertically to pulmonary orifice. Pulmonary valve indicated by white arrow. Decreased density and irregularity of anterior part of ventricle due to narrowing of cavity and trabeculations. Note striking dilatation of pulmonary artery and main branches. Bifurcation indicated by arrow.

moderate slowing of the blood flow from the arm to the pulmonary capillaries but a normal velocity between the lungs and the carotid sinus. Although such delay in the peripheral venous blood flow may occur in emphysema, according to Kountz and his associates,[2] it cannot be regarded as a

characteristic feature of *cor pulmonale*. Since the foregoing methods of study had failed to establish the diagnosis, it was necessary to employ roentgenology for the recognition of this disorder.

Fluoroscopic and roentgenographic examinations revealed the classical picture of *cor pulmonale* frequently seen in older patients in whom there is also arteriosclerotic or hypertensive heart disease.[29, 30] In the frontal view, the heart was low, centrally placed, and triangular in shape. This configuration was caused in large part by the rounded prominence of the right lower border which was almost a mirror image of the left contour; and the triangular appearance was enhanced by the striking enlargement of the pul-

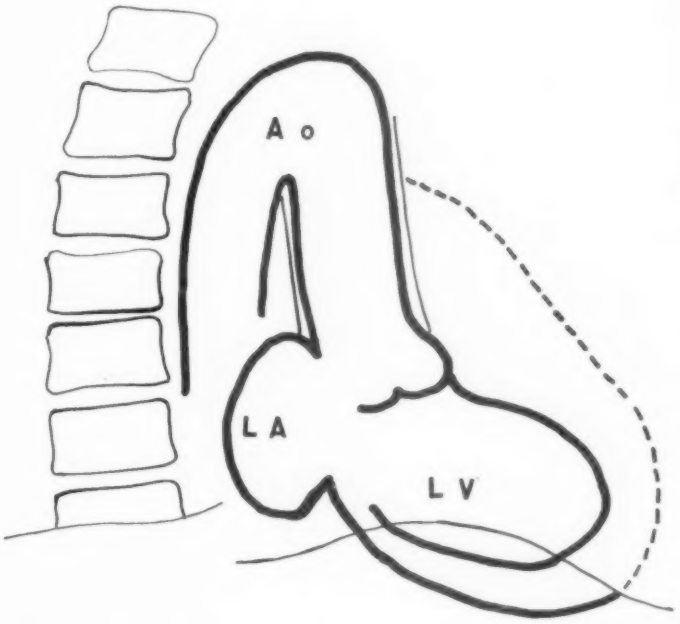

FIG. 7A. *Tracing.*
L. A. = left atrium; L. V. = left ventricle; Ao. = aorta. Note cusps of aortic valves and thickness of aortic wall.

monary arc which completely obliterated the usual concavity and replaced it by a convex bulge. Contrary to the observations of Dietlen [29] the pulsation of the lower right cardiac border and the pulmonary arc was not unusually forceful. The hilar blood vessels and their descending branches were increased in size and density as described by Clerc and Mourrut,[32] Parkinson and Hoyle [3] and others, but not to the degree frequently seen, and certainly not enough to merit the term "moustache." However, the smaller vessels were typical of pulmonary fibrosis and emphysema in that they were strikingly decreased in size and number and appeared stiff and wire-like in the middle and peripheral zones. Study in the oblique positions completed the

roentgenographic picture of *cor pulmonale*. In the right oblique view the pulmonary arc was strikingly prominent and angular; and the right branch of the pulmonary artery as it crosses the spine and the left receding branch were obviously enlarged. The long axis of the heart also appeared length-

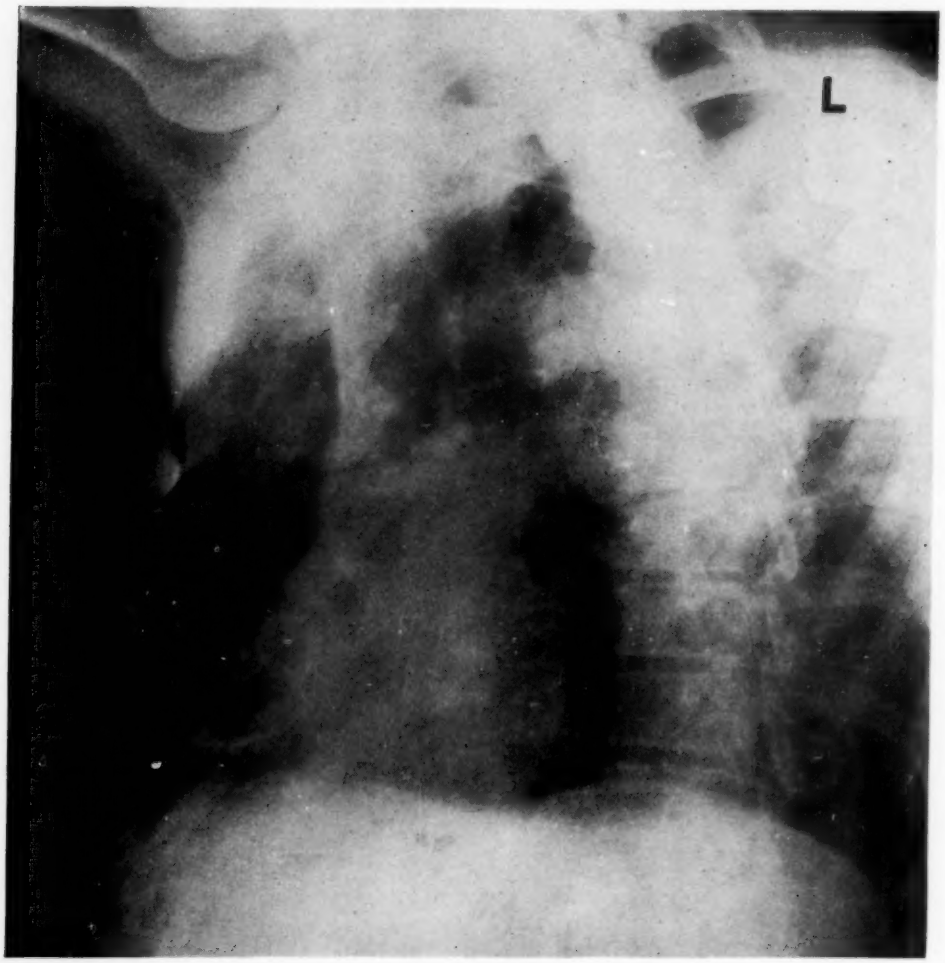

FIG. 8. *Conventional Roentgenogram—Left Anterior Oblique Projection.*
The right lower border of heart unusually prominent. Moderately enlarged aortic arch lies above; below is the conspicuously enlarged pulmonary artery with left branch almost filling "aortic window." Large oval density in pulmonary artery indicates receding right main branch.

ened in this view. In the left oblique position, the characteristic enlargement of the left branch was evident as this vessel crosses the "aortic window" beneath the unfolded aortic arch. These roentgenologic features in the presence of chronic pulmonary disease and the absence of mitral

stenosis, congenital heart disease, goiter, and myxedema heart warrant the diagnosis of pulmonary heart disease.

Although the evidence provided by conventional roentgenology has been invaluable in the diagnosis of this type of heart disease it, nevertheless, is relatively crude and gives but a poor insight into the condition of the heart and the pulmonary vessels. The significance of the changes in the size and the shape of the cardiac silhouette and of the pulmonary vessels has been established broadly by necropsy examination and postmortem visualization study, but interpretation in the individual case is difficult and inexact. It is known that right ventricular enlargement is manifested in the frontal view, first by prominence of the pulmonary arc due in part to upward elongation of this chamber and displacement of the pulmonary artery and, later, by transverse widening of the ventricle causing displacement of the right atrium to the right and of the left ventricle to the left and posteriorly. The boundaries of the right ventricle, however, cannot be determined accurately during life, and it is, therefore, impossible to estimate the degree of enlargement or to tell whether or not this chamber reaches to the right lower border of the heart or enters into the formation of the pulmonic arc. Likewise, the location of the pulmonary artery is indicated by the prominent pulmonary arc which it forms; but the size, the shape, and the course of the stem and the main branches cannot be seen in the frontal view, for they are concealed by the mediastinal and hilar densities.

The oblique views give better definition of the pulmonary artery and its branches, but these structures still are dimly outlined for only a short distance and neither their beginning nor end can be seen distinctly. At best, the anterior border of the main trunk is visible for only a few centimeters in the right oblique view, but its diameter and length cannot be determined and it is soon lost in the supracardiac shadow. Its right branch likewise is poorly defined (figure 5). In the left oblique position, the pulmonary artery cannot be recognized, but, because of the clear space termed the "aortic window" in this view, the left branch can often be seen.[3,30, 31, 41, 42, 43, 44] In both oblique positions the site of bifurcation of the pulmonary artery may frequently be identified by the rounded shadow which represents the receding main branch seen on end; the other branch crosses the lung field to disappear in the spinal density (figures 5 and 8). Angulation and prominence of the right cardiac border in the left oblique position is a reliable sign of right ventricular enlargement[41]; but it is obvious, since the location of the ventricular septum and the thickness of the right ventricular wall cannot be established, that any estimate of the degree of hypertrophy or dilation of this chamber must be very inexact. Similarly in the right oblique view, elongation of the long axis of the heart can be recognized, but it is impossible to know where the right ventricle begins and ends and how much it is enlarged. Since the pulmonary valves and sinuses are invisible, it is impossible to distinguish the pulmonary artery from the conus arteriosus and, therefore, to decide whether or not the conus reaches to the surface of the cardiac sil-

houette and is border forming. These and other important problems may now be solved by detailed visualization.

The advantages of visualization of the interior of the heart over ordinary roentgenologic examination have been illustrated by the contrast roentgeno-

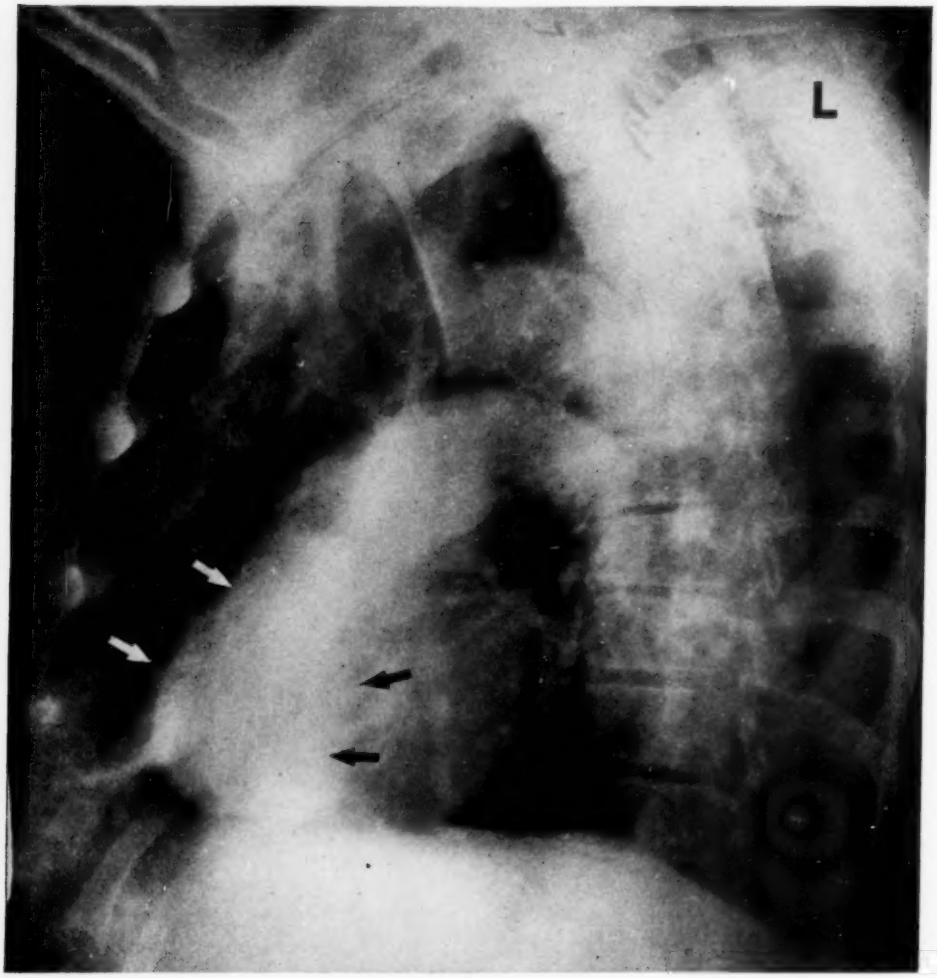

FIG. 9. *Contrast Roentgenogram—Left Anterior Oblique Position* at 4.5 seconds. Superior vena cava, right atrium, right ventricle, and enlarged pulmonary artery with main divisions filled. Upper black and lower white arrows embrace inflow tract of right ventricle. Lower black arrow points to beginning of outflow tract. Upper white arrow rests upon auricula and against conus arteriosus. Note ventricular wall thickness.

grams. Instead of an undifferentiated shadow of the heart and the larger vessels, visualization provides an accurate plan in which the size, the shape, and the location of each major structure can be seen. By the use of two or more projections, a three dimensional concept of each chamber and vessel may be obtained in which their complex anatomic relationships become dis-

cernible or at least better understood. As we have previously emphasized,[34] the frontal and lateral positions are ideal for visualization of the main stem of the pulmonary artery which is seen in end and side views respectively, and for the blood vessels at the hilum and in the lung. But because of the position of the heart within the chest, the oblique positions are essential for adequate study of the architecture of the heart, the right and left branches of the pulmonary artery and the aorta since these positions provide end and

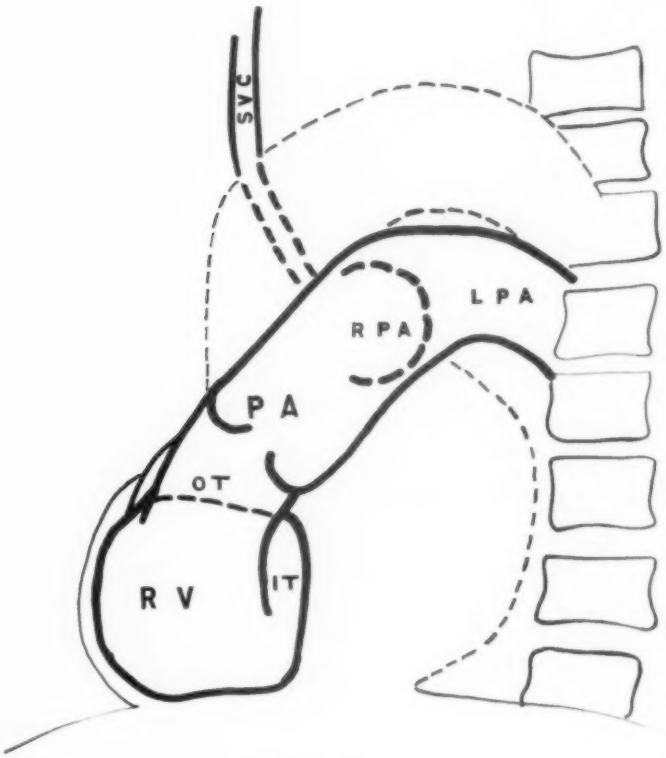

FIG. 9A. *Tracing.*

S. V. C. = superior vena cava; R. V. = right ventricle; I. T. = inflow tract; O. T. = outflow tract; P. A. = pulmonary artery; R. P. A. = right pulmonary artery; L. P. A. = left pulmonary artery.

Note pulmonary cusps.

lateral projections of these structures which are suitable for accurate interpretation and mensuration. Interpretation of the contrast roentgenograms in this case is based upon the evidence provided by Gray's Anatomy,[45] the anatomic and roentgenographic studies of Kirch,[20, 21] Vaquez and Bordet,[30] Nemet,[41] Nemet and Schwedel,[42] Assman,[31] Laubry and his associates,[40] Brenner,[39] Schwedel and Epstein,[43] Parkinson and Hoyle,[3] Rubin [44] and others, and upon our own postmortem study of other hearts. Direct confirmation by necropsy has not been possible since the patient is still alive.

The following detailed information regarding the heart, the great vessels and the pulmonary circulation was obtained in this case of *cor pulmonale*. The innominate and peripheral veins appear normal in size and location

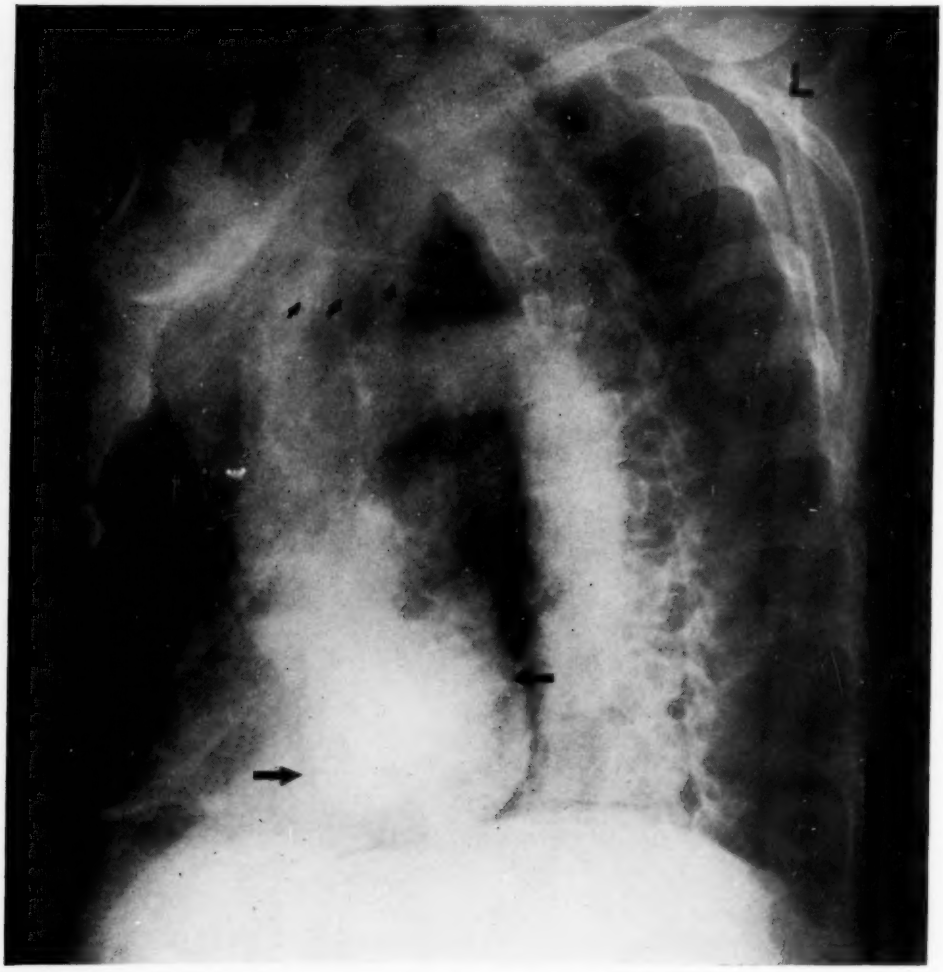

FIG. 10. *Contrast Roentgenogram—Left Anterior Oblique Projection* at 11 seconds.
Left atrium, left ventricle, thoracic aorta with vessels from arch well opacified. Black arrow near spine indicates left atrium; directly above is large pulmonary vein. Anterior arrow points to left ventricular cavity. Note elliptical density possibly due to stream from left atrium or overlapping of atrio-ventricular densities. Three main branches from aortic arch designated by small arrows. Note "aortic triangle" bounded by left subclavian artery in front, the spine behind, and the arch of the aorta below.

(figures 2, 2A, 6, 6A, 9, 9A, 12 and 12A). The superior vena cava also appears to be normal throughout its course (same figures). It begins in front of the second right costal cartilage and passes directly downward forming the right border of the supra-cardiac shadow to end in the right

atrium at the level of the third interspace. It lies well to the right of the ascending aorta midway between the sternum and the spine, and even with the posterior wall of the ascending aorta; it curves gently backward at the level of the pulmonary artery, and then forward again to enter the atrium.

The right atrium (figures 2, 2A, 6, 6A, 9, 9A, 12 and 12A) is normal in size, shape, and position. It is an oval structure lying at the level of the ninth and tenth thoracic vertebrae and resting almost upon the diaphragm. In lateral view of the heart (right oblique view) it lies directly behind and slightly above the inflow tract of the right ventricle from which

FIG. 10A. *Tracing.*

P. V. = pulmonary vein; L. A. = left atrium; L. V. = left ventricle; Ao. = Thoracic aorta; I. A. = innominate artery; L. C. A. = left common carotid artery; L. S. A. = left subclavian artery.

Black arrow points to density referred to in figure 9.

it is separated by the coronary sulcus (figure 6); it is slightly lower than the left atrium in all views (figures 6, 7, 9, 10, 12, 13). In the postero-anterior position the right atrium lies obliquely behind and to the right of the right ventricle, forming the lower right cardiac border (figure 2). This anatomic relationship is established by the absence of opacification of the atrium in figure 3, while the right ventricle is still outlined. In the left lateral projection (figure 12) the right atrium lies behind the center of the main cardiac shadow.

The right ventricle is enlarged in all diameters and its wall is moderately thickened (5 mm.). It is a roughly triangular cavity having a horizontal inflow tract which extends from the tricuspid orifice to the apex of the chamber; and a vertical outflow tract which reaches from the apex to the

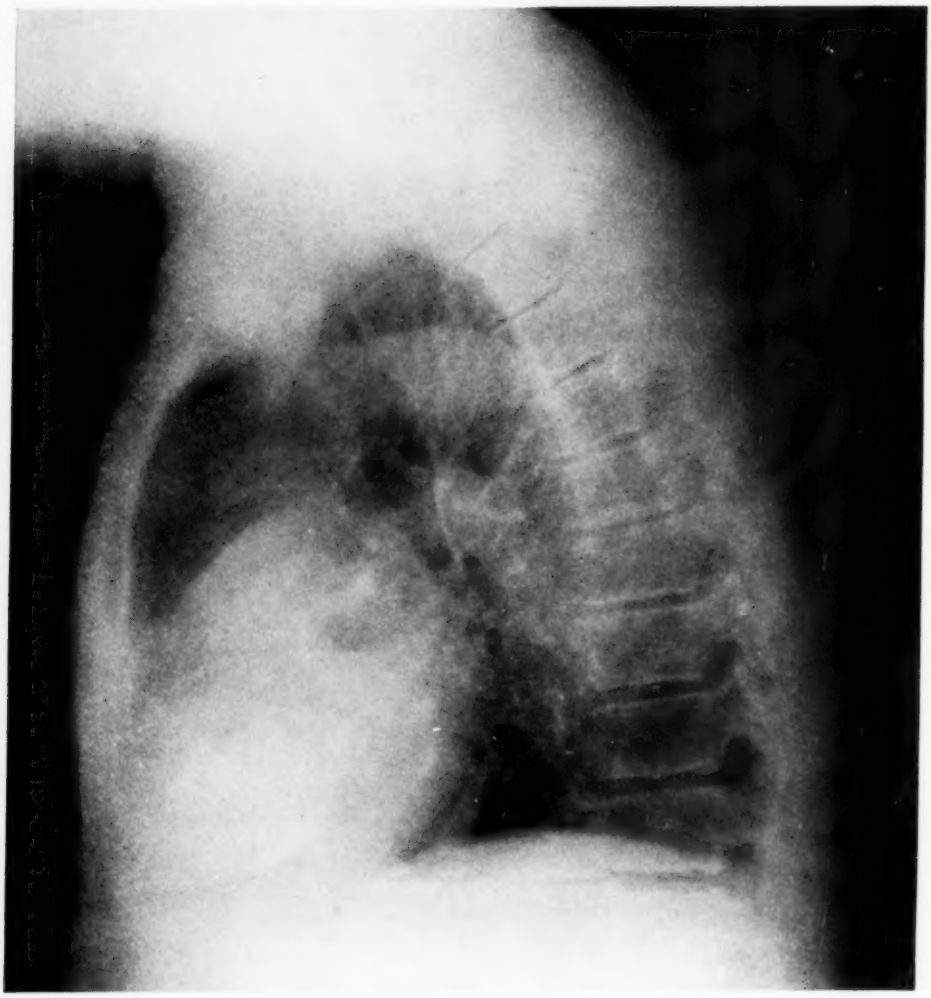

FIG. 11. *Conventional Roentgenogram—Left Lateral Projection.*

Note transverse enlargement of heart obliterating retrosternal space. Anterior border of pulmonary artery and left branch poorly outlined. Aorta appears moderately enlarged and its arch widened.

pulmonary orifice and ends as the conus arteriosus.[20, 21] Study of this chamber emphasizes the necessity for end and lateral views of the heart if a clear understanding of its anatomy and pathology during life is to be obtained. In the frontal position of the chest (figures 2, 3) there is fore-

shortening of the inflow tract and overlapping by the outflow portion, producing distortion and poor definition. Although the left lateral position of the chest (figure 12) gives a clearer picture of the structure of this ventricle and its relationships, there is still foreshortening and superimposition of structures. However, in the right oblique position (figure 6) which gives a side view of the heart, the right ventricular design is clearly shown. Both inflow and outflow tracts are seen without distortion and appear to be enlarged. The widened conus arteriosus plays but a minor rôle in the formation of the prominent pulmonary arc in this case (figure 6), since it forms only the lowest 2 cm. of that shadow.

The third dimension of the right ventricle is provided by the left oblique position which gives an end view of the heart in which the right chambers lie to the right, and the left atrium and ventricle to the left of the ventricular septum. On each side the ventricle lies in front and the atrium behind (figure 9). In this view the inflow tract, lying near the diaphragm, appears as a rounded body, since its long axis is directed toward the film and it is thus seen in cross section. There is marked enlargement of this cavity and only moderate thickening of its wall. The vertical outflow tract lying next to the film connects the near end of the inflow tract with the pulmonary artery above, and appears to be enlarged in length and breadth. Its terminal portion, the conus arteriosus, is widened but does not reach to the border of the heart as the right auricula forms the silhouette at this point. The thickness of the wall of the outflow tract can only be seen in the lateral projection (figure 12) in which the outflow tract forms the anterior border of the heart. Although the moderate increase in thickness of the right ventricular wall might lead one to conclude that little hypertrophy was present,[39] we believe that there must be a considerable increase in the mass of the right ventricle since this moderate thickening of the wall is accompanied by a conspicuous enlargement of the cavity and its surface area. The cusps of the pulmonary valve which can be seen in part in the frontal and both oblique views indicate with certainty the line of demarcation between the conus arteriosus and the pulmonary artery.

The pulmonary artery can be seen as a short broad tube which begins behind the interspace between the third and fourth left costal cartilages and, while curving slightly upward, passes directly backward toward the spine to bifurcate in front of the body of the seventh thoracic vertebra into its right and left branches (figures 2, 3, 6, 9, 12). The pulmonary sinuses lie just above the pulmonary valve and are visible in all projections except the frontal. The diameter of the pulmonary artery in this patient is strikingly enlarged, although there is no appreciable increase in its length. In the frontal view, part of its prominence, however, is due to elevation and displacement toward the left side by the enlarged right ventricle and part to the shadow of its left branch which caps that of the main artery and blends with it (figures 2, 3). Since the pulmonary artery passes directly posteriorly, it is seen best in the lateral position (figure 12).

Both right and left main branches can be seen in all positions but most distinctly in the oblique projections in which they are seen in end and side view. The left branch arches slightly upward from its origin and then passes posteriorly and downward to divide at the left hilum into superior

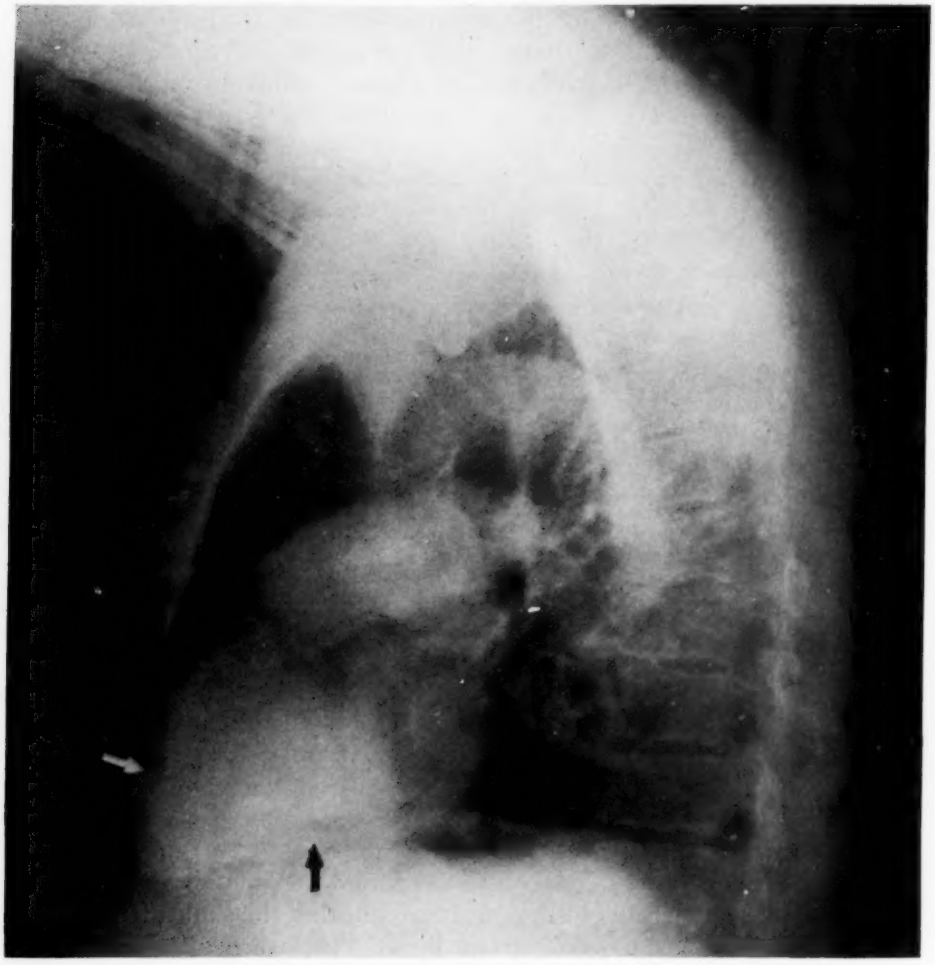

FIG. 12. *Contrast Roentgenogram—Left Lateral Projection* at 4.5 seconds.

Superior vena cava, right atrium, right ventricle, pulmonary artery, and both main trunks outlined. Black arrow indicates junction of right atrium and right ventricle which are partially superimposed. Directly to the right is inferior vena cava and immediately above is right atrium. Right ventricle lies anteriorly, the wall of the outflow tract indicated by white arrow. Conus arteriosus and pulmonary valves lie above. Note position of pulmonary arterial branches.

and inferior branches; whereas the right branch goes slightly downward and backward but predominantly transversely to end at the right hilum by dividing into two major branches. These vessels are all enlarged. Attention has already been called to the characteristic narrowing and diminution of the

smaller arterial branches seen in the middle and outer zones (figure 3). The pulmonary veins appear rather small and decreased in number but otherwise are not remarkable in this study. They are not seen to advantage, as figure 4, the frontal position, shows the contrast substance has already traversed these vessels. The veins, however, may be seen converging toward both sides of the superior pole of the left atrium (figure 7).

The left side of the heart requires little comment. The left atrium appears to be entirely normal. The left ventricular wall, however, lies at the

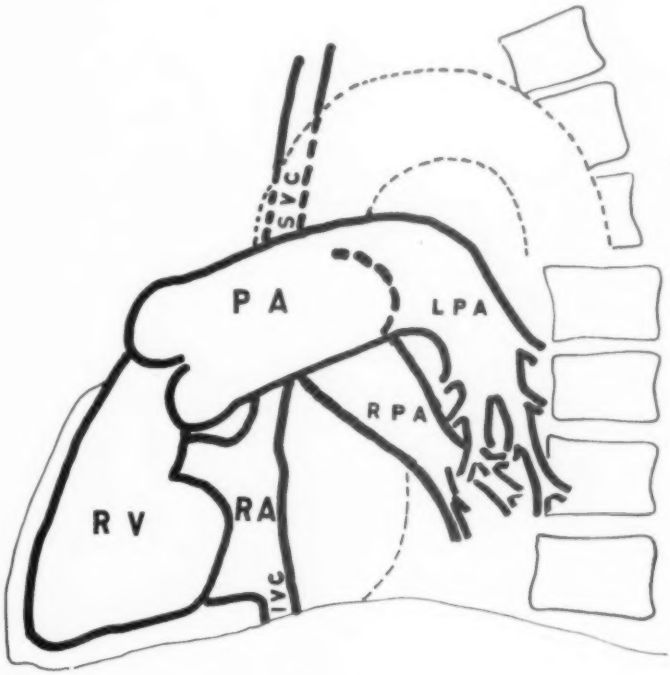

FIG. 12A. *Tracing.*

S. V. C. = superior vena cava; R. A. = right atrium; I. V. C. = inferior vena cava; R. V. = right ventricle; P. A. = pulmonary artery; R. P. A. = right pulmonary artery; L. P. A. = left pulmonary artery.

Note excellent definition of pulmonary artery seen here in side view; and relationship of right and left branches.

upper limit of normal thickness (figures 4, 10) and the ventricular cavity is slightly enlarged (figure 10) but there is no abnormal development of the left ventricular contour (figures 4, 10). This moderate degree of hypertrophy is probably due to coronary artery disease [44] or chronic myocardial anoxemia [2] since arterial hypertension can be excluded as a factor. The double border near the apex remains a puzzle (figure 4). The innermost contour appears to be continuous with the inner surface of the left ventricle while the middle curve almost bisects the wall. It is possible that there is a circumscribed thinning of the ventricular wall at this point due to a previous

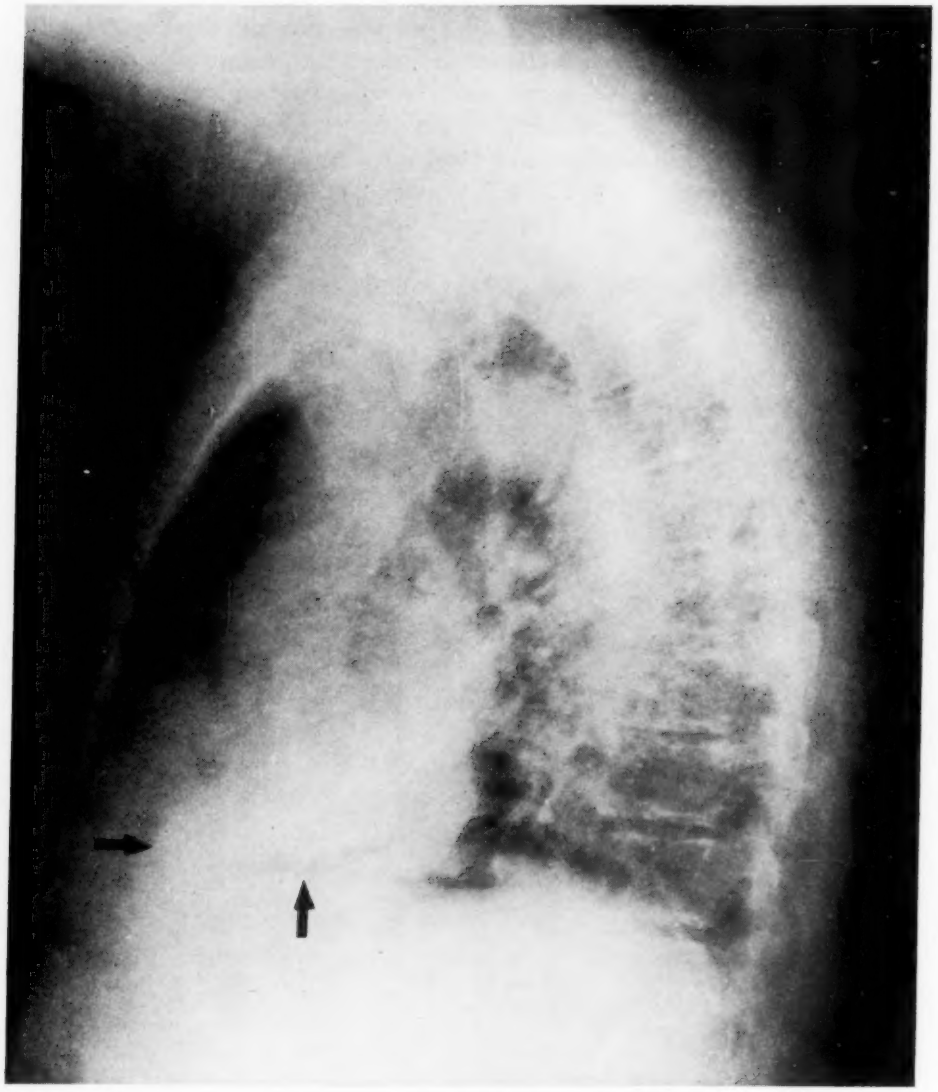

FIG. 13. *Contrast Roentgenogram—Left Lateral Projection* at 11 seconds.

Left atrium, left ventricle, and thoracic aorta opaque. Inferior arrow points to overlapping area of atrium and ventricle. To right lies atrium with vein entering superior pole, to left is left ventricle, and between them a denser shadow possibly caused by blood flowing through mitral valve or overlapping of atrio-ventricular densities. Anterior arrow shows extent of ventricular cavity; immediately above is aorta with dilated sinuses. Note excellent view of aortic sinuses in this position.

myocardial infarct, although there is no history to suggest this explanation and no electrocardiographic evidence to support it. Finally, it is possible, although we believe it unlikely, that this extra line of density may be an artefact. The aorta shows only a moderate degree of dilatation and thickening of its wall, and of elongation, tortuosity and "unfolding" in its course through the thorax. The innominate, the left common carotid, and the left subclavian arteries, likewise, are enlarged and tortuous (figures 4, 4A, 10 and 10A). The "aortic triangle" [50] which is formed by the aortic arch inferiorly and the spine posteriorly is clearly outlined in figure 10, and

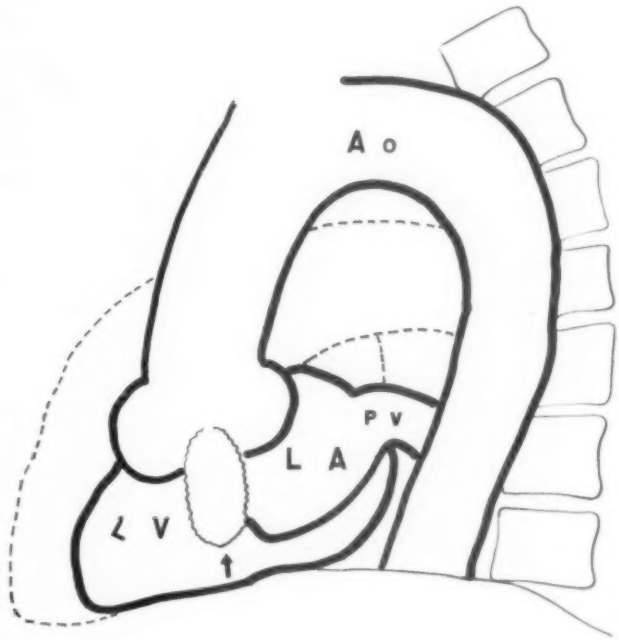

FIG. 13A. *Tracing.*
P. V. = pulmonary vein; L. A. = left auricle; L. V. = left ventricle; Ao. = aorta. Arrow indicates oval density referred to in figure 13.

its anterior boundary is shown to be the left subclavian artery, a fact heretofore not demonstrated during life.

A comparison of the conventional methods of cardiovascular mensuration and the detailed measurement permitted by visualization leaves no doubt as to the greater worth of the latter method. In this obvious case of *cor pulmonale* the conventional methods, it is true, indicated a moderate degree of cardiac enlargement and considerable dilatation of the pulmonary artery, although accurate evaluation of heart size was impossible since our observations were made with the chest in the full inspiratory position instead of the mid-position used in the establishment of the normal standards.[25, 47, 48] However, the broad diameter, the transverse diameter, and the frontal area

of the heart were certainly greater than the expected normal value [47, 48] and the width of the aortic arch and the chord of the aorta lay at the upper limit of the normal.[30] Moreover, the pulmonary artery, too, was strikingly enlarged, as indicated by the transverse index of Vaquez and Bordet [30] which measured 5.8 cm. as compared with their normal range of 2.7 to 3.2 cm. and the pulmonary " flèche " of Abreu [49] which was 13 mm. as compared with the normal limits of 1 to 5 mm. Valuable as these data are, they nevertheless give an imperfect picture of the structural state of the heart. Visualization obviates the use of such arbitrary diameters of the cardiac shadow which have no anatomic counterpart, and makes possible the measurement of fundamental anatomic structure such as the height, the width, and the depth of each chamber, the diameter and the length of the larger vessels, and the thickness of the cardiac and the vascular walls. Comparison of these measurements with the normal standard will ultimately permit the precise localization of the disease and accurate estimation of its degree, although at present precise appraisal of each part is impossible since our observations in the normal are yet too limited to permit the establishment of comprehensive standards. However, it is obvious in this case that the right ventricular cavity and wall and the pulmonary artery and its branches are conspicuously larger than any counterpart in our series of normal subjects; whereas the left ventricular wall is only slightly thickened and the thoracic aorta is moderately dilated, elongated, and thickened.

Summary

Visualization of the chambers of the heart and the thoracic blood vessels was performed in a patient with pulmonary heart disease due to chronic bronchitis, pulmonary fibrosis, and emphysema in order to demonstrate the pathological changes occurring in this condition and the value of detailed visualization in its diagnosis. A three dimensional picture of cardiovascular structure and relationships was obtained by study in the frontal, the lateral, and the two oblique positions.

This case study emphasized the well-known fact that pulmonary heart disease cannot be recognized from history, physical signs, or electrocardiographic changes but requires roentgenographic evidence. Conventional roentgen-ray examinations disclosed the typical picture of *cor pulmonale* found in older persons with emphysema and independent heart disease. The enlargement of the right ventricle and the pulmonary artery and its branches was revealed by the prominence of the right lower cardiac border, the pulmonary arc, and the hilar shadows in the frontal view, and by the accentuation of the right ventricular contour, the pulmonary arc, and the right and left pulmonary arteries in the other positions. But conventional roentgenology could not define the boundaries of the right ventricle and the pulmonary artery or show how much these structures entered into the formation of the cardiac silhouette.

Detailed cardiovascular visualization, however, revealed the size, the shape, and the position of each chamber and the diameter and the course of the great vessels and the pulmonary circulation. The superior vena cava and both atria were entirely normal and the left ventricle and the aorta were only moderately enlarged; whereas the right ventricle and the pulmonary artery were conspicuously enlarged. Both inflow and outflow tracts of the right ventricle were involved and showed dilatation of their cavities and thickening of their walls. The conus arteriosus, which was distinguished from the pulmonary artery by the pulmonary valve, played no immediate part in the formation of the prominent pulmonary arc in the frontal view, although it was border forming for a short distance in the right oblique view. The outflow tract appeared to form the entire anterior cardiac border in the lateral view.

The exaggeration of the pulmonary arc in this case is due to two factors: elongation of the right ventricle upward and to the left with displacement of the pulmonary artery in these directions and marked enlargement of this vessel itself. The pulmonary arc is formed exclusively by the pulmonary artery except in the frontal position in which the upper half centimeter of this curve is caused by the arching left branch of this vessel. The accentuation of the hilar shadows is due to enlargement of the main branches of the pulmonary artery and their larger subdivisions while the decrease in lung markings in the mid and outer zones of the lungs is due to narrowing and obliteration of the smaller vessels.

Conclusions

1. Detailed visualization of the cardiovascular system demonstrated for the first time during life the nature and the extent of the pathological changes in pulmonary heart disease.

2. Cardiovascular mensuration may now become an exact procedure since it can measure fundamental anatomic structures rather than arbitrary diameters having no anatomical counterpart.

3. The recognition of the early stages of pulmonary heart disease which hitherto could not be diagnosed should now be possible.

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UNTOWARD EFFECTS FROM THE USE OF ERGOT AND ERGOTAMINE TARTRATE *

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ERGOT preparations have enjoyed a time-honored place in obstetrical practice. In properly standardized dosage they have come to be accepted as useful oxytocics when administered after expression of the placenta; they promote uterine involution and prevent postpartum bleeding and puerperal sepsis. Since isolation of the crystalline alkaloid, ergotamine, described by Spiro and Stoll [1] in 1921, numerous clinical entities have been treated by the specific ergot alkaloids. At one time in the past decade, approximately 80 medical disorders of one kind or another were enthusiastically treated with ergotamine tartrate. Peptic ulcer, migraine, pruritus, diabetes mellitus and insipidus, hyperthyroidism, glaucoma, various hemorrhagic tendencies, melancholia, epilepsy, and cord bladder of taboparetic origin, all may be mentioned as examples of disease states appearing to respond to this form of medication. The calming effect of time and of a few well-directed clinical and physiologic studies [2] has gradually hewn this vast array of therapeutic indications in the field of internal medicine down to a very select group of conditions, the chief of which are migraine [3] and pruritus.[4]

Amazing controversies have been waged in the medical literature of the past decade as to the fundamental pharmacologic effects of ergotamine. That its effects are significantly different from those of ergotoxine, which was discovered by Barger and Carr [5] in 1906, can no longer be maintained.[6] The original and fundamental observation by Barger and Dale [7] that ergotoxine has a stimulatory effect on smooth muscle holds true in the light of present knowledge, and the same applies to ergotamine. Both drugs are stimulants to the heart, arteries, intestine and uterus. Increases in blood pressure and intestinal peristalsis are thus secondary.[8] Interesting speculation has arisen over Dale's discovery of "vasomotor reversal," that is, the elevated blood pressure produced by an injection of ergotoxine may be slightly and transiently lowered by an injection of epinephrine. That an important factor in the relief of migraine by ergotamine is its vasoconstricting property has recently been indicated.[9]

A rational explanation for the occasional marked relief obtained in cases of pruritus by the use of ergotamine is not clear. The popular hypothesis heretofore has been that ergotamine partially paralyzes the sympathetic nerve endings whose irritability is responsible for the pruritus. Another explanation for this curious phenomenon of relief suggests itself: It is a well-known clinical observation that any constant pruritus is more severe when there is an increased room temperature and is less severe when there is a

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decreased room temperature. Cooling lotions frequently also are of assistance. Ergotamine is known to produce a fall in peripheral temperature [10] and to produce decreased peripheral blood flow [11] by means of its vasoconstricting power. The converse has been noted, that injection of histamine in cases of atopic dermatitis produces an elevation of the temperature of the flexural surfaces with an associated localized pruritus.[12] All of this suggests that the relief of pruritus by ergotamine is in some way related to its cooling effect on skin temperature.

Barger [13] has described in great detail the complications that follow the administration of ergot, having traced them through medical history from medieval times. Two types of ergotism have been described: One type, in which peripheral gangrene develops, seems clear cut; the other type, in which so-called epidemic convulsions occur, is not so clear cut. The convulsive type of ergotism originated in famine districts where cereals were the chief source of nutrition, and it was associated with cataracts, massive edema, peripheral skin changes, and psychoses but not with gangrene. Stockman [14] was able to isolate toxic salts of phytic (inosite hexaphosphoric) acid, definite neurotoxins, from several cereals which, when injected hypodermically into monkeys fed on a low vitamin diet, would produce a picture strikingly similar to that known as "convulsive ergotism."

Untoward Effects from the Use of Ergot as Recorded in the Literature

In the modern medical literature there are few reports of cases of toxicity following the use of ergot. Oldright [15] in 1870 described a case in which there were "first, symptoms of spasm of the arterioles with dizziness, syncope and surface coldness followed by congestion of the face and head." Meadows [16] mentioned symptoms of marked depression, nausea, headaches, and swelling of the hands in a case in which the patient was given ½ dram (1.85 c.c.) of powdered ergot. The same dosage was given three weeks later and the same symptoms recurred in an exaggerated form. Later, the same dose produced only mild toxic symptoms. Keating [17] described a case in which through a misunderstanding the patient took ½ dram doses of a fluidextract of ergot every half hour for four hours. Cyanosis, dyspnea, nausea, thready pulse, dilated pupils, and powerful uterine contractions developed, but the patient responded rapidly to circulatory stimulants. Hulme [18] gave one teaspoonful of Squibb's fluidextract of ergot to a 48-year-old woman with menorrhagia. Forty minutes later, the patient's hands, face, and abdomen became swollen, her pulse became rapid, weak, and irregular, the pupils were dilated, and nausea, dizziness, and blurred vision were complained of. Moskowitz's [19] patient, who received 1 dram (3.7 c.c.) of the fluidextract of ergot three times daily to promote postpartum uterine involution, suffered from coldness, cyanosis and weakness of all extremities on the sixth day. While the heart appeared to be normal and the brachial

and femoral arteries were not involved, there was complete absence of pulsations in both radial, popliteal, and dorsalis pedis arteries which persisted for 60 hours after prompt discontinuation of ergot medication. Meanwhile, pain and impending gangrene appeared in each foot and there was some subsequent sloughing of part of one foot. In these five cases the drug was administered for therapeutic purposes and in at least one of the cases, that of Keating, the dosage was larger than that ordinarily given.

Untoward effects from the use of ergot in attempts to produce abortion are especially interesting because of the severity of the symptoms. Davidson [20] reported a case of attempted abortion in which two handfuls of powdered ergot had been taken in one dose. Among other symptoms, jaundice of the upper extremities was described. Necropsy revealed numerous hemorrhages in the viscera and small ruptured blood vessels. Kobert [21] cited four cases of fatal attempts to produce abortion with ergot. He described subcutaneous icterus with sudden blackness and numbness of extremities and subsequent mummification. McKay [22] described a case in which the arms became painful and the fingers swollen, painful, and cyanotic and finally gangrenous following the ingestion of a large quantity of liquid ergot in an effort to produce abortion. Amputation of the parts was ultimately necessary. Rosenbloom and Schildecker's [23] patient had become unconscious after attempting abortion with ergot; loss of bowel control, urinary suppression, chronic convulsions, and visible uterine contractions developed. The stools were bloody and contained sloughed intestinal mucosa. Necropsy revealed punctate hemorrhages throughout the intestinal mucous membrane.

Untoward Effects from the Use of Ergotamine Tartrate as Recorded in the Literature

The number of cases in which definite vasospastic phenomena and peripheral gangrene of the type seen in ergotism have occurred and in which ergotamine may be definitely considered as an etiologic factor is not large. These cases may be grouped according to the condition for which ergotamine was given:

Puerperal Sepsis. A considerable number of cases of puerperal sepsis in which ergotamine tartrate was administered and in which gangrene developed has been recorded. Since peripheral gangrene occurs infrequently in puerperal sepsis when ergot is not used, many have discounted the rôle of ergotamine in causing the gangrene. Saenger [24] reviewed 13 cases in 1929 and assumed that ergotamine tartrate was not the principal cause of the peripheral gangrene; he concluded that the appearance of gangrene was due in all cases to infectious toxic changes in the vessels. He felt that if ergotamine had played a part it was a secondary one. A review, however, of such cases as the following can lead only to the conclusion that ergotamine has played a significant rôle at least in some of the cases of puerperal sepsis in which gangrene has appeared:

Case 1 (*Oginz* [25]). A primipara, aged 19 years, with puerperal sepsis was given 6 drams (22 c.c.) of fluidextract of ergot and a total of 45 c.c. (22.5 mg.) of gynergen subcutaneously over a period of 11 days. On the seventh day postpartum, coldness and cyanosis of the extremities developed, and there was complete disappearance of the radial pulse. The heart action, however, was exceptionally good. By the tenth day the extremities were cold and there was excruciating pain in the right foot; the toes and plantar surface first became blue, then green, and later black. Twenty-four hours after gynergen medication was discontinued, the upper extremities became warmer and the radial pulse returned. Pain in the right foot continued to be severe and a line of demarcation appeared in the right foot on the sixteenth day. The foot improved with baking and local treatment but, four months later, it was necessary to amputate the stumps of the first three toes and probe a discharging sinus in the ball of the foot.

The prompt improvement in the vascular condition following discontinuation of gynergen therapy strongly suggests that the gynergen, and not the puerperal sepsis, was responsible for the accident.

Case 2 (*Roch* [26]). A woman, aged 23 years, suffered from chills, fever, and uterine discharge five days after cesarean section. She was given 20 drops of ergotamine tartrate twice daily for four days (total dose estimated to be 10.6 mg.). On the third and fourth days there was painful pallor of all extremities. The arterial blood pressure in millimeters of mercury was 80 systolic and 60 diastolic. On the fifth day the pain became more intense in all extremities, particularly in the left foot. The temperature was 38.7 to 39.5° C., the heart beat was regular and rapid, the pulse not perceptible, and the left foot was extremely painful, with splotchy white and purple discolorations of the anterior third. The toes were cold, violaceous, and had the appearance of impending gangrene; the right foot and both hands had the same general appearance, although the condition was less marked. Next to the livid areas the skin was pale and cold. The patient complained of spontaneous paresis and paresthesias and increased pain to the slightest touch. There was complete anesthesia of the toes of the left foot. Arterial pulsations were not perceptible. It was impossible to determine the blood pressure in the arm, forearm, thigh, or leg. Blood cultures were negative. The diagnosis of ergotism was arrived at by elimination. The patient was treated with spasmalgine (containing both papaverine and atropine derivatives) and acetylcholine. The symptoms were ameliorated after 24 hours. On the third day of treatment, the blood pressure could be taken in all four extremities. The extremities appeared to be normal except for the left foot where there was definite gangrene. It was later necessary to amputate a portion of this left foot.

Again the prompt response to the discontinuation of the drug and to the administration of vasodilating drugs points strongly to ergotamine as the cause of the condition.

Case 3 (*Polano* [27]). A woman, aged 36, who had tuberculosis showed evidence of uterine infection following a therapeutic abortion performed during the third month of pregnancy. The patient received postoperatively 1 mg. of ergotamine orally three times a day for five days. The radial pulse was not palpable on the seventh day and on the fourteenth day there was definite dry gangrene of the left hand.

The disappearance of the radial pulse prior to the onset of symptoms of ischemia again suggests that the vasospastic action of ergotamine was the first manifestation of the impending gangrene, a circumstance hardly to be expected if the infectious process was responsible.

Menorrhagia. Case 4 (Brack [28]). A woman, aged 30 years, with marked nervousness and menorrhagia, was given a total of 24 mg. of ergotamine hypodermically over a period of 42 days. On the twenty-fifth day of medication a progressive numbness of all the fingers developed. On the fortieth day the patient complained of severe, knife-like pains and of a withering sensation in her fingers and she was unable to bend them without aid. Small doses of scopolamine and dial partially controlled the symptoms, but they persisted for three weeks after discontinuation of ergotamine medication.

Hyperthyroidism. Case 5 (Schönbauer [29]). A woman, aged 28 years, suffering from exophthalmic goiter, was given 0.5 c.c. (0.25 mg.) of ergotamine hypodermically twice daily for seven days, with 1 c.c. twice daily on the eighth and ninth days. On the ninth day there were pain and cramping of the lower extremities with swelling and discoloration of the right foot and toes. The toes rapidly became livid, cold, and pulseless, showing absence of pulsation by capillary microscopy. By the fifteenth day the gangrene had become dry and more sharply demarcated.

Case 6 (*Platt* [30]). A girl, aged 16 years, with hyperthyroidism was given subcutaneously a total of 20 mg. of ergotamine in 23 days. Administration of ergotamine was promptly discontinued on the appearance of severe muscular cramps of the lower extremities, with coldness, numbness, pain, and cyanosis of the entire right foot and left big toe. Scopolamine, grain 1/150 (0.0004 gm.) by hypodermic injection, produced slight improvement, but the cramps persisted for three weeks.

Case 7 (*Speck* [31]). A woman, aged 29 years, who had thyrotoxicosis, was given a routine preliminary treatment with ergotamine which consisted of 93 tablets (46.5 mg.). After an interval of three weeks, a second course of ergotamine was instituted. On the sixth day a furry sensation was noted in both legs, and abdominal pain, diarrhea and severe pain and coldness in both legs were noted on the eighth day. The following day the feet were cold, slightly blue and tactile sensation was diminished. Ergot poisoning was suspected and administration of the ergotamine was discontinued. The patient had then received 27 tablets (13.5 mg.) of ergotamine. Despite contrast baths, atropine, and the intravenous injection of theophylline, sodium acetate and sodium nitrite, the appearance of impending gangrene increased to definite demarcation in the lower part of the legs. On the sixteenth day, sensation improved and the feet were warmer. Marked improvement occurred in the next few weeks with a return of blood supply and this Speck attributed to the theophylline. Six months later there were some residual symptoms of stiffness in the right ankle joint and some thickness on the back of the right foot.

Case 8 (*Zorn* [32]). A woman, aged 39 years, suffering from exophthalmic goiter, was given postoperatively 15.5 mg. of ergotamine tablets over a period of eight days. There was sudden development of pain and numbness in both lower extremities on the eighth day. The feet were cold and there was beginning gangrene. Arterial pulsations could not be felt on either side. The patient was treated with contrast baths and 1 c.c. injections of padutin (pancreatic extract) daily for three days. The peripheral pulsations returned and the symptoms cleared entirely.

Case 9 (*Müller* [33]). A woman with Basedow's disease was given 24 c.c. of ergotamine suocutaneously over a period of 18 days and, simultaneously, roentgen treatment over the thyroid gland. On the sixteenth day a violent sensation of pain and coldness developed in both lower extremities. The right foot turned a mottled, purplish color and there was indurated swelling of the lower part of the right leg. The pain and cramps became intense. On the eighteenth day the administration of ergotamine was discontinued. Despite all treatment, dry gangrene with demarcation had involved all toes on the right foot. In the next six months most of the toes dropped off spontaneously, but it was necessary to amputate the right big toe. Pain in the right leg persisted for a total of seven months and then entirely disappeared.

Jaundice and Pruritus. Case 10 (Yater and Cahill [34]). A man, aged 64 years, suffering from jaundice and severe pruritus, was given 1 c.c. (0.5 mg.) of ergotamine tartrate by subcutaneous injection three times daily for six and a third days (a total of 9.5 mg.). On the second day of administration, coldness was noted in the upper extremities. By the fourth day there was coldness and blueness of the distal third of both feet. Two days later symptoms were much more definite; faint pulsations were felt in the dorsalis pedis arteries. There was definite gangrene of the toes of both feet on the thirteenth day. Bilateral amputation of the distal portions of both lower extremities was performed one month after the onset of the gangrene. The extremities were studied arteriographically and pathologically.

Case 11 (Gould, Price, and Ginsberg [35]). A woman, aged 52 years, suffering from jaundice and pruritus, was given 0.5 c.c. (0.25 mg.) of ergotamine tartrate, subcutaneously, daily for four days (a total of 1 mg.). After the second ampoule, pain and coldness developed in the legs. On the third day cyanosis, coldness, and impaired sensation of the lower two-thirds of both legs developed. On the fourth day, pulsations of the dorsalis pedis and radial arteries could not be felt. A blood pressure reading could not be obtained. The heart sounds were regular and of fair quality. Examination of the ocular fundi showed arterial narrowing which was not present at the time of admission. Despite the administration of glyceryl trinitrate and amyl nitrite the lower two-thirds of the legs became gangrenous. The patient became semistuporous and died on the following day. At necropsy all the arterioles examined were found to be contracted.

Case 12 (Perlow and Bloch [36]). A 36-year-old man with Hodgkin's disease, jaundice, and pruritus was given 1 mg. of ergotamine by mouth and 2.5 mg. subcutaneously over a period of six days. On the evening of the last injection there was pain in the toes, and the next day morphine was required for relief of increasing pain in the toes. The toes were cyanotic, cold, and slightly ischemic. On the following day pulsations could not be felt in either the dorsalis pedis or posterior tibial arteries. The peripheral skin temperatures were markedly decreased. Several injections of papaverine hydrochloride, ½ grain (0.032 gm.) intravenously caused a rapid return of the feet to a normal appearance with normal peripheral arterial pulsations and skin temperature.

Other Conditions. Vascular accidents other than thrombosis of the peripheral vessels and gangrene have been described. Labbé, Boulin, Justin-Besançon, and Gouyen [37] described a case of Basedow's disease in which three subcutaneous injections of ergotamine produced, first, an attack of anginal pain and, later, hemiplegia. Zimmermann [38] described a prolonged fatal anginal attack occurring a few minutes after injection of one ampoule of ergotamine and he reviewed the effect of gynergen on the heart. He has also described a case of toxic goiter in which ergocholine produced auricular fibrillation, lasting from a few minutes to two hours, and with a ventricular frequency from 150 to 170. The patient had definite evidence of diffuse myocardial damage. The toxic symptoms described by Panter [39] were unusual: in his case tinnitus, absence of deep reflexes, and fixed pupils persisted for a week after ergotamine therapy (nine ampoules having been given in three days). Baber and Tietz's [40] patient died after having received 2 mg. of ergotamine daily for three days. Pulmonary infarctions were found in this case.

Untoward Effects from the Use of Ergotamine Tartrate at The Mayo Clinic

The following two cases in which untoward symptoms developed from the use of ergotamine tartrate were personally observed by us:

Case 1. A woman, aged 59 years, registered at the clinic October 1, 1934 complaining of painless jaundice and pruritus. A diagnosis was made of partial obstruction of the common duct due to stricture. The jaundice was marked. The systolic blood pressure in millimeters of mercury was 160 and the diastolic 90. General physical examination otherwise gave essentially negative results as did examinations of the urine (except for bile), blood, and serologic test for syphilis.

The patient was hospitalized on October 3. Ergotamine tartrate in oral doses of 1 mg. three times a day, was prescribed for the pruritus and this symptom was controlled after the first two days of medication. A 10 per cent solution of glucose in amounts of 1,000 c.c., and 10 per cent calcium chloride, in amounts of 5 c.c., were given intravenously on the fourth, fifth, sixth, and seventh days. On October 4, the bleeding time was four minutes, the coagulation time (Lee and White) three and a half minutes, and the concentration of bilirubin in the serum 20 mg. per 100 c.c.; the van den Bergh reaction was direct. It is worthy of note that local venous thrombosis occurred with the injections on October 5 and 6.

On October 10, the condition of the patient had markedly improved. The concentration of bilirubin in the serum had dropped to 11 mg. per 100 c.c.; the bleeding time was unchanged, whereas the coagulation time had decreased to two minutes, an abnormally low figure for a patient so deeply jaundiced. Surgical intervention was planned; however, about noon, the patient complained of pain and numbness in her right hand which had become quite blue. The extremities were cold, and the patient was unable to recognize tactile or thermal stimuli applied to the right hand. The administration of ergotamine tartrate, of which a total of 23 mg. had been given, was then discontinued at the onset of these symptoms. The application of local heat to the extremities was followed by apparent improvement. That evening, however, the patient's condition became worse. She was restless, apprehensive, and weak. All four extremities were cold. The cyanosis of the right hand and wrist had become more marked, and the patient could not move the fingers of the right hand. Pulsations could not be felt in the left ulnar or in the right radial and ulnar arteries, and only slightly in the left radial artery. The pulsations of both brachial arteries appeared to be normal, but pulsations of the arteries of the feet were weak. Blood pressure readings could not be obtained in the arms. The cardiac impulses definitely increased in intensity.

The next morning, the patient still complained bitterly of pain in both hands and arms. The color of the right hand remained unchanged. Arterial pulsations had entirely disappeared below the level of the elbow in each arm and were felt with difficulty in the vessels of the feet. It looked as if gangrene of the right hand would develop (figure 1). Continuous, hot, moist packs were applied, however, and massage in the direction of the hands was done for 15 minutes of each hour. Ephedrine, grain ¾ (0.05 gm.) was given every two hours.

The patient was fairly comfortable during the night, but on the morning of October 12 looked drowsy and vomited. The condition of the extremities remained the same. The treatment was then altered. The extremities below the elbows were wrapped in cotton batting. The hands were kept slightly lowered and the patient was given 15 c.c. of alcohol every four hours. Venous cyanosis but no arteriospasm was found on examination of the ocular fundi. On October 13 some improvement was noted. There was little, if any, change in the condition of the right hand, but pulsations could be felt in the left radial artery. The patient stopped vomiting and ate a little breakfast.

On October 14, pulsations could be felt in all the vessels of the upper extremities and pulsations in the feet were much more easily felt. The purplish discoloration of the right hand had largely disappeared and the temperature of both hands appeared to be normal. Blood pressure readings were obtained for the first time, the systolic blood pressure being 118 and the diastolic 84. The pulse rate was 80 beats per minute. The temperature rose to 100° F. and an edematous swelling of the right hand appeared.

By October 15 further improvement was noted. The dorsum of the right hand and wrist was edematous and dusky (see figure 1). The bleeding time was two

FIG. 1. (Case 1). Photograph taken October 15, 1934 during the height of the brawny edematous swelling of the right hand.

minutes, the coagulation time was still unchanged. By October 19 the jaundice had cleared perceptibly. The value for serum bilirubin was 3 mg. Tactile sensibility was diminished grade —3 to —4, and pain perceptibility, grade —1 to —2 (on a basis of 1 to 4) over most of the surface of the right hand. The movements of the fingers of the right hand were markedly diminished in range and speed, those of the wrist less so. By October 22, the patient's condition had improved so much that she was permitted to return home.

Soon after this the jaundice reappeared and the patient returned to the clinic on December 7. Her right hand was still stiff, and muscular atrophy (grade 2) and

paresthesias were present (figure 2). The coagulation time had increased to four and a half minutes. A diagnosis was again made of partial obstruction of the common duct due to stricture and of post-thrombotic contraction with atrophy of the right hand. Exploration was carried out on December 10. A stricture of the common duct, apparently 2 cm. in length, was found, excised, and an end-to-end anastomosis was made between the hepatic and common ducts. The postoperative convalescence was uneventful. Further improvement in the condition of the right hand followed persistent physiotherapy (see figure 2).

Case 2. A woman, aged 50 years, first registered at the clinic on May 21, 1934 at which time a radical left mastectomy was performed for adenocarcinoma, grade 3, which measured 3 cm. in diameter. The lymph nodes were found to be involved. A year later simple amputation of the right breast was performed for diffuse mastitis. The patient last registered at the clinic on January 20, 1936, complaining of jaundice

FIG. 2. (Case 1). Photograph taken December 28, 1934 showing residual atrophy of the right hand.

which had come on painlessly about a month previously. Pruritus was marked and the patient was hospitalized for examination. One to three tablets of ergotamine tartrate daily controlled the pruritus. A diagnosis of metastatic carcinoma of the liver was made. On January 28, the radial pulses could be palpated only with the greatest difficulty and the administration of ergotamine tartrate, of which 16 mg. had been given, was discontinued. On the next day the pulses became more easily palpable although they were still small in volume. On the second day after administration of the ergotamine tartrate had been discontinued both radial pulses returned to their normal full volume.

The cumulative toxic, vasoconstrictive action of ergotamine tartrate is well illustrated in these two cases. In the first case, vasoconstriction was followed by thrombosis, ischemic neuritis, and late secondary contracture.

In the second case, vasoconstriction was the sole manifestation of toxicity. In each case the administration of ergotamine tartrate was discontinued as soon as toxic symptoms developed and recovery followed, prompt recognition of the nature of the condition and prompt institution of treatment undoubtedly being responsible for the excellent recovery in each case. In the first case vasodilating drugs contributed to the recovery.

Experience in these two cases led us early to adopt the practice of routine palpation of the arteries of the extremities several times daily during the administration of ergotamine tartrate and in this way further unhappy experiences have been avoided. In this connection, it is interesting that Gaysinovich [41] and his coworkers who have had a wide experience with ergot poisoning resulting from the ingestion of ergot-infested rye bread, have noted a pregangrenous state capable of complete regression, similar to that in these two cases.

The first case was unusual in another respect. In this case tests of coagulation of the blood showed a tendency to rapid coagulation instead of slowed coagulation, as one would expect in the case of a deeply jaundiced patient. It is interesting that the coagulation time was decreased during treatment with ergotamine tartrate and that thrombosis finally occurred. The effect of ergotamine on the coagulation time of the blood in this case is not clear.

General Considerations

Dosage. Untoward effects sometimes occur after the administration of very small doses of ergot or ergotamine tartrate. Hulme reported toxic symptoms after a teaspoonful of fluidextract of ergot had been given. In Gould, Price, and Ginsberg's case, toxic symptoms appeared soon after the hypodermic administration of a second daily dose of 0.25 mg. of ergotamine tartrate. Only an idiosyncrasy to the drug can explain such effects. Most untoward reactions, however, occur after larger doses and apparently result from a cumulative action of the drug. When ergotamine has been given hypodermically, untoward effects have occurred following doses varying anywhere from 0.5 to 24 mg. When the drug has been given orally, the total amount of the drug administered is somewhat larger and has varied between 10 and 60 mg. In Speck's case the patient tolerated a course of ergotamine therapy consisting of 93 tablets (46.5 mg.) but, after an interval of three weeks, marked vascular symptoms developed after only 13.5 mg. of ergotamine tartrate had been given. That the sensitivity of the individual to ergotamine varies widely is emphasized by the fact that some patients have taken the drug in the usual doses over periods of weeks and even months without untoward symptoms developing, others require two or three times the usual dosage if therapeutic results are obtained, and still others have developed symptoms of ergotism following only small doses of the drug.

Contraindications. Many who have written on obstetrical subjects have expressed the belief that ergot is contraindicated in sepsis. Caffier [42] be-

lieved that puerperal infection produced toxic injury of the blood vessels and that ergot might produce gangrene more readily in the presence of these changes. The histologic studies of Lewis and Gelfand [43] have shown that peripheral vascular thrombosis rapidly follows the intimal damage of ergot. It does not seem unreasonable that thrombosis and gangrene should occur more frequently when two conditions capable of producing intimal damage and thrombosis are active simultaneously.

The untoward effects described by Labbé, Boulin, Justin-Besançon, and Gouyen, and Zimmermann emphasize the danger of administering ergot to individuals who have cardiac disease. Its administration is also thought to be contraindicated in the presence of vascular disease.

Symptoms. The earliest symptoms of ergotism are headache, nausea, vomiting, diarrhea, tinnitus and vertigo. These are the untoward symptoms that have followed the hypodermic injection of ergotamine tartrate in cases of migraine and, when they occur, indicate that smaller doses may be used effectively. Dilatation of the pupils and blurring of vision are also toxic symptoms, and in cases of poisoning by massive doses, unconsciousness and incontinence or suppression of urine, convulsions, sloughing of intestinal mucosa, and bloody diarrhea have been described. Jaundice and cyanosis occur infrequently.

In those cases in which vasospastic phenomena develop the earliest finding is disappearance of the pulse, as in Polano's and our second case. Pain, particularly muscular cramping, peripheral paresthesia, decreased skin temperature, and perhaps pallor (as in the case of Breck) are followed by the appearance of cyanosis, discoloration of the skin, and actual thrombosis; gangrene is a still later development. Cerebral and gastrointestinal symptoms may develop simultaneously with the peripheral vascular condition. Closure of the vessels, with cyanosis, apparently may take place suddenly. If gangrene does not develop, the condition may regress, leaving contracture of the muscles. If gangrene develops spontaneously, amputation of the affected part may occur or surgical amputation may eventually become necessary.

Diagnosis. It is most important to emphasize that the approach of ergotism should be suspected as soon as the pulsation of the vessels diminishes perceptibly in the case of any person receiving ergot or ergotamine. The diagnosis should be clear as soon as any of the peripheral pulses disappears or as soon as paresthesias, pallor, or cyanosis develop.

Prognosis. Of the 14 cases of ergotism following the use of ergotamine which have been reported, gangrene occurred in seven and death in one. The prognosis seems to depend to some extent on what stage the process has reached when it is recognized and when administration of the drug is discontinued. It is significant that gangrene developed in only two of the eight cases in which the administration of ergotamine tartrate was discontinued as soon as the symptoms or local findings attracted the physician's attention. In contrast to the comparative rarity of gangrene under these

circumstances was the development of gangrene in five of six cases in which the administration of ergotamine tartrate was continued after symptoms or local changes had occurred. Gangrene does not necessarily follow the appearance of cyanosis. In four cases administration of the drug was discontinued after the affected parts had become discolored. Ischemic neuritis and contracture of the muscles may persist after the circulation is reestablished.

Treatment. Prophylactic measures are several in number: (1) the avoidance of the use of ergot in sepsis and cardiac or vascular disease; (2) its administration only under the close supervision of a physician; (3) awareness on the part of both the physician and patient of early toxic manifestations; (4) careful daily observation of the size of the peripheral vessels while the patient is receiving ergot or its derivatives, and (5) discontinuation of the use of the drug when the pulsations of the vessels perceptibly diminish and on the appearance of the first untoward and bizarre symptoms of muscular cramping or paresthesia.

Vasodilating drugs are indicated as soon as the first symptoms of ergotism appear. Gaysinovich recommended 1 c.c. of 1 per cent pilocarpine solution subcutaneously for its fast dilating effect in addition to the use of daily intravenous administration of 15 to 20 c.c. of 3 per cent magnesium sulfate solution. Rubin and Rapoport's [44] experience with magnesium sulfate parenterally in the control of hypertension and gangrene induced by the administration of ergotamine likewise points to the value of this drug in the treatment of ergotism. Acetylcholine, as suggested by Roch, might prove helpful. Alcohol [45] is an effective vasodilator, particularly of the vessels of the upper extremities, and is a helpful sedative in this condition. Papaverine,[46] in doses of ⅓ to ½ grain (0.02 to 0.032 gm.) is a well-known and a usually effective vasodilator, especially when given intravenously, and may provide some analgesia. Cleansing enemas should be given when ergotamine has been given orally. The rationale of giving scopolamine, epinephrine, and ephedrine is open to question.

Summary and Conclusions

Untoward effects from the use of one of the preparations of ergot or of ergotamine tartrate hitherto reported in the literature have been briefly reviewed. To these we have added two cases personally observed by us in which untoward effects developed following the use of ergotamine tartrate for the control of pruritus.

Some of the untoward effects that have been reported have followed administration of doses larger than those compatible with good practice. In other cases, however, such effects have followed the use of very small doses and have apparently been dependent on the existence of an individual idiosyncrasy to the drug. In still other cases such untoward effects have followed the use of the drug in the usual dosages and were apparently due to a cumulative action of the drug.

In spite of these many instances of ergotism it is not our intention to discourage administration of ergotamine tartrate in doses of proper size provided adequate precautions are taken. The drug has proved itself too valuable for this, especially in the control of pruritus and migraine. Instead, we would emphasize the contraindications to its use, the danger of the development of ergotism, and point out that the onset of ergotism may be suspected early by frequent examination of the arteries of the extremities for spasm and by recognition of its early symptoms.

Prompt and early recognition of ergotism and the discontinuation of ergot or ergotamine tartrate medication, followed by the administration of such vasodilating drugs as pilocarpine subcutaneously, magnesium sulfate parenterally, and alcohol orally, are the prerequisites for the avoidance of irreparable damage.

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VITAMIN A CONTENT OF THE HUMAN LIVER IN TUBERCULOSIS *

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The vitamin A content of human livers was determined photometrically in 50 patients in whom tuberculosis was the cause of death. The vitamin A content of their diet averaged from 5,000 to 8,000 U.S.P. units per day. All patients were fed the general hospital diet, except those with tuberculous enteritis. These were given a modified ulcer or soft diet of a similar vitamin A content. Six patients were given a supplemental dosage of vitamin A.

The findings were evaluated according to the average vitamin A content per gram of liver, age, supplemental dosage, duration and febrile course of manifest disease and the presence of tuberculous enteritis.

Method

The total liver weight was noted. To a 100-gram portion of finely ground liver, 500 c.c. of potassium hydroxide (5 per cent) were added. This mixture, after standing 48 hours, was heated to boiling for 30 minutes, cooled and extracted eight times with ether. The combined extracts were washed three times with distilled water, or until the washings were not alkaline to litmus. The extract was dehydrated with anhydrous sodium sulphate, filtered and evaporated to dryness under vacuum. The residue was weighed as unsaponifiable matter and spectrophotometric determinations made with a Hilger Vitameter.

Results

The liver contents of vitamin A ranged from essential depletion (less than 3 U.S.P. units of vitamin A per gm.) to a maximum of 1640 units per gm. The average for the 50 cases was 342 units per gm. The average content according to age is given in table 1. The six patients who received a supplemental dosage of about 70,000 units of vitamin A per day, over periods of one to three months, averaged a vitamin A liver content of 628 units per gm., as compared with 313 units for the patients having no other source of vitamin A than the hospital diet. Included in this group is a patient who received 10,700,000 units of vitamin A over a period of 120 days. This individual came to autopsy three years later following a fulminating case of pulmonary tuberculosis of one year's duration. During the interim the patient was on the hospital high vitamin A diet. The spectrophotometric analysis revealed only 64 units of vitamin A per gm. of liver.

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The vitamin A content per gram is essentially the same, regardless of the duration of the disease. Patients with a febrile course in excess of 100° F. reveal the vitamin A content of the liver reduced about 50 per cent, as compared with the cases having febrile courses below 100° F. The vitamin A content of the latter type of case compares favorably with the average found for normal persons. Hospitalization on the high vitamin A diet contributed to a moderate increase in the liver content of vitamin A. This increase was of about one-third, and was fully manifest within 100 days of hospital stay.

Intestinal tuberculosis was a clinical feature in 36 per cent and a gross pathological finding in 44 per cent of the cases. Patients with enteritis averaged 180 units of vitamin A per gm., as compared with 313 units for those with no evidence of this complication.

In this series, one patient manifested essential depletion of vitamin A as shown by the liver analysis. Seven patients averaged less than 30 units per gm. and 16 had less than 100 units per gm. of liver. Thus, half of all the patients had less than one-third of the vitamin A reported for normal persons. All patients with enteritis were below the average for the series, as well as the average for normal individuals.

Discussion

The average liver content of all patients (342 units per gm.) compares favorably with that reported (331 units) in a previous paper [1] for healthy persons. The vitamin A liver content in the present group demonstrates that the average finding is far from the saturation point, as evidenced by the wide variation between it and individual cases. The average is about one-fifth of the maximum finding.

The distribution according to age is not significant, except for the fact that in older individuals the vitamin A content is somewhat increased (table 1). The abundant nutrition given phthisical patients and the prolonged duration of the fibrotic disease would account for these results.

From experimental work on dogs, the authors [2] estimated that approximately 1800 units of vitamin A were utilized daily by a normal, average human being. The hospital diet thus offers 3 to 4.5 times the average intake. The high vitamin diet of the tuberculosis hospital furnishes sufficient vitamin A for storage, whether it is absorbed or not. This might well explain the increased liver content of vitamin A in the cases of prolonged hospitalization, which is fully manifest within 100 days (table 1). The patients surviving less than 100 days, having either far advanced or fulminating disease, exhibit a more marked pyrexia and usually a terminal enteritis. The increased metabolic rate, due to the pyrexia and the enteritis, with faulty absorption, tends either to prevent or deplete the usual vitamin A supply of the body. Those surviving less than one year show but little

TABLE I

Vitamin A Content of Human Liver in Tuberculosis—50 Cases

	Number of Cases	U.S.P. Units per Gm. of Liver
AGE RANGE:		
15–20 years	4	684
20–30 years	18	276
30–40 years	8	226
40–50 years	11	219
50–60 years	6	430
60 and over	3	532
DURATION OF DISEASE:		
Less than one year	25	295
More than one year	25	285
PYREXIA:		
Below 100° F	26	423
Above 100° F	24	253
HOSPITAL DAYS:		
Less than 100 days	29	237
More than 100 days	21	358
Less than one year	38	352
More than one year	12	304
ENTERITIS:		
Absent	32	423
Present	18	180
AVERAGE	All Cases	341
Minimum	Less than 3 units per gm.	
Maximum	1640 units per gm.	

difference from those surviving 100 days. All patients with enteritis were below the average and many approached depletion.

SUMMARY

1. The average vitamin A content of human livers in 50 cases of tuberculosis was 342 U.S.P. units of vitamin A per gm. The minimum was practically depletion (3 units) and the maximum was 1640 units per gm. of liver.

2. The vitamin A content of the human liver approached depletion in 14 per cent of the patients.

3. Administration of generous doses of vitamin A is indicated in tuberculosis with pyrexia or enteritis.

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THE RÔLE OF SYMPTOMS AND SIGNS IN AMEBIASIS *

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The belief prevails among many clinicians that symptoms and signs associated with amebiasis, particularly when subjective and objective deviations are not readily attributable to other factors, indicate that such changes are due to *Endameba histolytica.* The earlier parasitological viewpoint as expressed by Craig [1,2] was not dissimilar. Our experience of more than a decade with clinical-parasitological problems denotes that this is not wholly true. The parasitological viewpoint in recent years has become similarly modified as evidenced in Craig and Faust's [3] later writings. Thus, many carriers † of *E. histolytica* are in reality symptomless; in some others, the vaguer or more general symptoms and signs ordinarily attributable to this parasite when it is encountered, do not seem to be caused by it; not all diarrheas and dysenteries with which *E. histolytica* is associated can be said definitely to have been brought about by it. It is our impression, because of the type of inquiries often made of us by practitioners, that clinical knowledge in this connection lags behind the protozoölogical. Hence the presentation of the following data to emphasize the clinical problems involved, and the possible interpretation of symptoms and signs in relation to amebiasis.

Clinical Data

Group I. Those with *E. histolytica* in the stools, without symptoms, with and without signs.

A. Those with Endameba histolytica without symptoms and signs. Six women, five white and one colored, and four men, three white and one colored, whose ages ranged from 16 to 26, were discovered during the course of examinations on defecated specimens of feces routinely performed upon successful applicants for hospital positions, to harbor *E. histolytica.* Upon this finding, they were reëxamined with a view toward ascertaining any symptoms and signs which might have borne some relationship to this infection. All data, including repeated history and physical examination, as well as blood count, blood Wassermann, urinary examinations, roentgenoscopic study of the chest and digestive apparatus, gastric analysis, as well as rectosigmoidoscopy, were completely negative.

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† The expression "carriers of *E. histolytica,*" as used in this paper, refers to individuals harboring *E. histolytica* which commonly appears in their stools as cysts, but who do *not* seem to be experiencing symptoms such as loose or frequent stools, intestinal bleeding, etc., presumably due to the presence of the parasite.

All were given carbarsone (Lilly, 4-carbamino-phenyl-arsonic acid: 28.8 per cent arsenic) 0.25 gm., twice daily for ten days. Seven were observed over six months, during which three specimens of saline-purged feces were examined monthly. The remainder were seen over a lesser time. In this group, the parasite was never encountered in any specimen subsequent to carbarsone administration. Subjectively and objectively, all were well before and after treatment.

B. Those with Endameba histolytica and without symptoms. A group of 10 food handlers—encountered during a protozoölogic survey—were discovered to have cysts of *E. histolytica* in defecated specimens of feces. It was only possible to ascertain that all had no symptoms; uncontrollable circumstances prevented objective study.

GROUP II. Those with *E. histolytica* in the stools with symptoms and signs.

A. Those without diarrhea and dysentery. Nine men, seven white and two colored, and six women, five white and one colored—a total of 15—whose ages ranged from 20 to 60, who came to the gastrointestinal section of the Johns Hopkins Hospital for relief from various and sundry abdominal complaints but who had no diarrhea or dysentery, were found to harbor *E. histolytica* in defecated specimens of feces. Submitted to the type of study already referred to, they were found to be free from demonstrable organic disease but some manifested changes in digestive tone or gastric secretion. It had been taught that there was an etiologic relationship between the presence of this parasite and such complaints. Indeed, this impression still prevails among many clinicians. It was hypothesized by us that if this were true, complete eradication of the parasite should result in elimination of complaints. Thereupon, each case was given 0.25 gm. carbarsone per os, twice daily for 10 days. They were observed over six months during which three specimens of saline-purged feces were examined monthly. With the exception of one case, the parasite was never encountered in any specimen subsequent to carbarsone administration. This exceptional instance responded eventually to a repeated course of carbarsone and one course of vioform (iodochloroxyquinoline). Suffice it to say that carbarsone gave relief from symptoms in the majority for a maximum of three weeks following its prescription. In all cases, long before the six month period had elapsed, and in the face of parasite eradication, similar symptoms had recurred with at least equal severity and prominence. These symptoms were then adequately controlled by antispasmodics, sedatives and hypnotics. Cessation of these measures resulted in undiminished recurring symptoms even in the continued absence of *E. histolytica.* Symptoms again subsided upon the reinstitution of this type of pharmacotherapy. Objectively, alterations in tone and secretion were not constant and did not parallel subjective relief.

There is no satisfactory explanation for the transient relief coincidental with carbarsone administration. This has been seen not infrequently—

during the course of this study—in cases with vague abdominal symptoms in which *E. histolytica* could never be demonstrated. Can it be ascribed to the tonic influence of arsenic? Can it be ascribed to psychotherapy? If the latter were completely true, one would have expected at least one case to be markedly benefited for six months—the duration of the observation period.

B. Those with diarrhea and dysentery. This communication is not concerned with those cases presenting symptoms among which are diarrhea or dysentery associated with *E. histolytica* in which there is complete relief from subjective and objective manifestations upon the eradication of the parasite. Such are cases of true amebic diarrhea, amebic dysentery, or amebic colitis. They are clearly understood and need no further comment.

Special attention is directed here to the type of case which has, among other complaints, dysentery or diarrhea but in which after eradication of the parasite, there is no complete cessation of the subjective and objective picture.

A case in point is as follows: A 19 year old white male, American born, entered the Johns Hopkins Hospital on November 22, 1933, with a history of three or four bloody, liquid bowel movements daily for the last two months. Objectively, *E. histolytica* and an ulcerative colitis were encountered. A diagnosis of amebic dysentery was made. He was given adequate courses of yatren, carbarsone, and emetine hydrochloride. The parasite was never encountered upon repeated examinations but his colitis persisted with little improvement as late as January 6, 1936, more than two years later. When last seen on April 2, 1937, the bowel was better but much muco-pus was still in evidence and the involved tissue was very friable.

Cases of this type, some with greater improvement, are infrequent but not rare; they have been referred to by Kiefer,[4] Craig[5] and Meleney and Frye.[6] At present, it is not possible to say when the presence of *E. histolytica* is primarily, partly, or not at all responsible for symptoms and signs in such instances for the following reasons:

Five to 10 per cent of the population are said to be infected with *E. histolytica*, most of them healthy carriers. Is it not possible that one or more of these individuals may develop colitis on an entirely different basis? Unless there is some antagonism between amebic colonization and the non-amebic colitides, the theoretical expectation, based upon the amebic prevalence cited above, is that from 5 to 10 per cent of the persons with non-amebic colitis should harbor *E. histolytica* fortuitously. How, then, can this be differentiated from the type of colitis in which *E. histolytica* is the causative agent, and in the eradication of which "cure" does not result? Also, is it not possible to acquire the parasite subsequent to the initiation of a colitis non-amebic in origin? Clinical improvement (not complete relief) upon amebicidal therapy cannot be used to determine the rôle of *E. histolytica* under these circumstances. Non-specific ulcerative colitis sometimes responds similarly to amebicides: clinical improvement occurring without complete relief. Also, pharmacotherapeutic knowledge of amebicides in the

complete relief of amebic involvement, does not permit any definite deductions as to the significance of its effectiveness in part.

Interpretations and Summary

1. A study was undertaken to evaluate the rôle of signs and symptoms in human amebiasis. Ten individuals were found to harbor *E. histolytica* and —as far as modern diagnostic methods were able to ascertain—were well subjectively and objectively before and after amebicidal therapy. In them, at the time of study, the presence of *E. histolytica* was not incompatible with good health.

2. Fifteen cases found to harbor *E. histolytica* presented digestive symptoms which heretofore had been ascribed to this protozoön. Eradication of the parasite did not eliminate symptoms and signs. The symptoms were controlled by antispasmodics, sedatives and hypnotics, and recurred—in the absence of this parasite—when these pharmacotherapeutic measures were withdrawn, and were again relieved by their re-administration.

3. Finally, the rôle of signs and symptoms in amebiasis is to be determined by the response to specific therapy. If there is complete, not partial, response, subjectively and objectively, upon amebicidal therapy coincidental with eradication of the parasite, then it may be said that there was a cause and effect relation between parasite and host manifestations. Our present knowledge does not permit the etiologic evaluation of *E. histolytica* in the production of signs and symptoms when the clinical responses to amebicides are partial in the face of parasitologic eradication. Thus, given a colitis or dysentery plus *E. histolytica*, it appears not to be possible to say that *E. histolytica* is the prime causative agent unless there is complete (not partial) subjective and objective response to specific therapy.

4. There is nothing in this communication which is to be construed as indicating that those harboring *E. histolytica* should not be treated. Parasite eradication should always be undertaken from the standpoint of prevention and as a public health measure.

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INTERSEXUALITY OR PSEUDO-HERMAPHRODISM *

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It is generally assumed that the sex of an individual is determined at its inception by specific genetic factors, but in order for the genetically determined sex to be expressed anatomically, certain conditions must prevail during the developmental period. The sex-hormone complex which plays an important rôle in the development of sexual structures is normally in accord with the genetic factors so that development proceeds toward the expression of the genetically determined sex. However, alteration in the sex-hormone complex can result in modification of the normal course of sexual differentiation so that abnormal conditions may arise.

The anatomical expression of sex does not occur until relatively late in development. Up to this stage in development the embryo is in a sexually indifferent stage, i.e., every embryo, regardless of its future sex, has all the anlage necessary for development in either the male or the female direction. In normal male development the indifferent gonad differentiates into a testis, at the age of six or seven weeks. The Wolffian duct is stimulated and differentiates into its component parts, the epididymis, vas deferens, seminal vesicle and ejaculatory duct. The Müllerian duct, on the contrary, degenerates except for some nonfunctional remnants. The urogenital sinus and genital tubercle are stimulated to produce prostate glands, Cowper's glands, a male type of urethra, the scrotum and a penis. In normal female development the gonad differentiates into an ovary. The Müllerian ducts are stimulated to develop into oviducts, uterus, and upper vagina, while the Wolffian ducts degenerate. The urogenital sinus and genital tubercle develop in the female direction and the lower vagina, female urethra, Bartholin's glands and external female genitalia are formed (figure 1—normal development).

It is believed that the sex hormones are important in the normal process of sexual differentiation. Good evidence for the profound influence of sex hormones on sexual differentiation has been obtained in amphibia and birds. The earlier experiments involved gonad grafts and parabiosis (the fusion of two embryos so that their vascular systems are confluent). In later years, since the isolation of the various sex hormones in the crystalline form, the technic of hormonal injection into the incubating egg or the amphibian

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embryo has been used.[1-7] In these experiments evidence was obtained that the male hormone caused sexual differentiation in the male direction and that

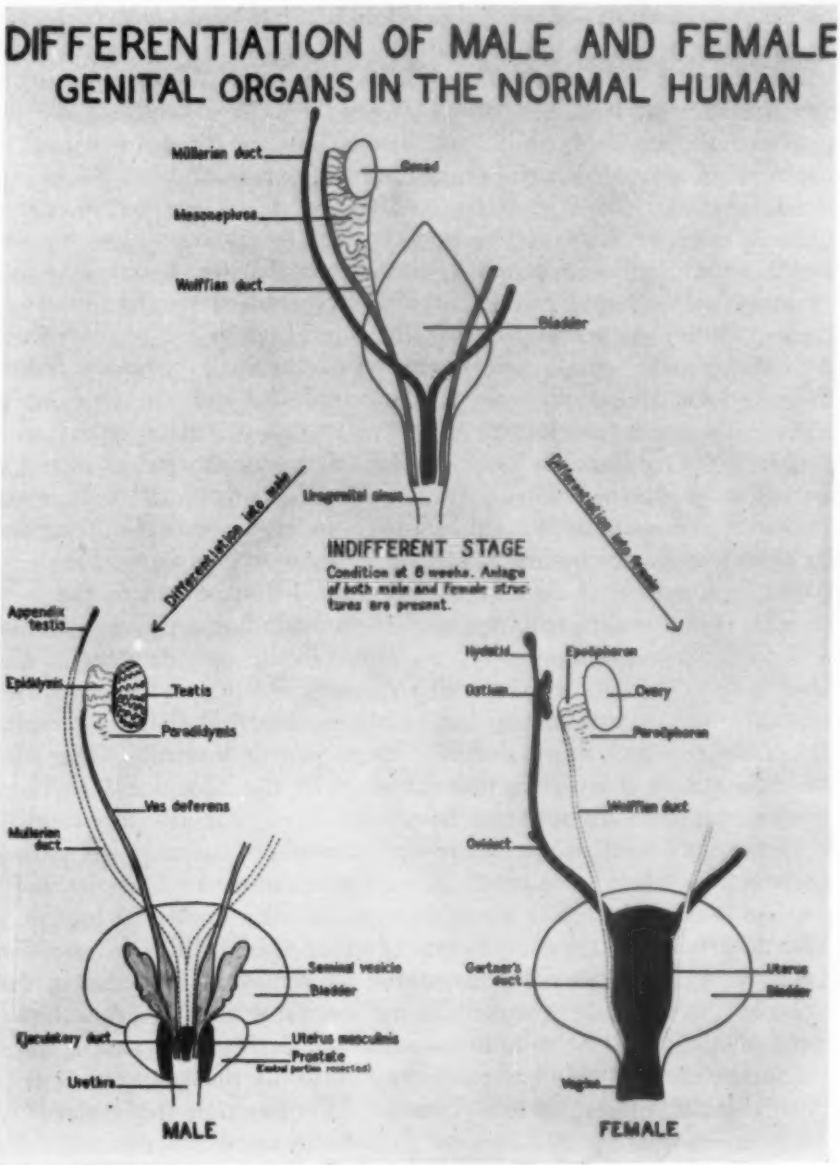

FIG. 1.

the female hormone caused differentiation in the opposite or female direction.

The mammalian embryo is not an isolated and self-sufficient unit as are

the embryos of the bird and amphibia. Therefore, until recently the mammalian embryo has been considered to be inaccessible for similar hormonal experimentation. However, in mammals, good evidence of the effect of the male hormone on embryonic sexual development has been obtained by study of the naturally occurring free-martin in cattle. Twins are not uncommon in cattle. Frequently, because of the diffuse nature of the placenta in these animals, vascular anastomoses occur between the twin placentae. When the twins are of the same sex, both are normal. When they are of opposite sex the male is normal, but the female is always masculinized. This masculinized female is the free-martin. The gonads of the free-martin are testicular-like in structure. The duct system is more or less completely masculinized while the external genitalia are usually feminine. Lillie,[8] Keller and Tandler,[9] and other workers have studied the free-martin extensively. Lillie has postulated that the alteration in the sexual development of the genetic female twin is caused by the male hormone produced in the male twin and transferred to the female through the vascular anastomosis. Two facts are known which make this postulate appear reasonable. First, the mammalian embryo, in its development, passes through an indifferent stage during which the anlage for both male and female structures coexist, and secondly, the male embryo undergoes sexual differentiation earlier than the female. Thus the male hormone which is produced in the male twin is transferred through the common blood stream to the female. The female is still undifferentiated so that the male hormone has a chance to mold the still plastic structures of the embryo in the male direction.

On the basis of evidence obtained from experiments on lower forms and from studies on the free-martin, it has been theorized that differentiation of the gonads is probably primarily under genetic control. The rest of sexual differentiation is, then, under control of the hormones produced by the gonads. That differentiation of the gonads is not influenced solely by genic factors has been shown by numerous workers inasmuch as partial or complete sex reversals—the production of testes instead of ovaries and vice versa—has been obtained in amphibia and birds by hormonal injections.[1-7]

The *dihormonic theory*, or the theory that sexual differentiation in the male is influenced by male hormone, and in the female is influenced by female hormone has been widely accepted for the lower forms. Wiesner, however, has promulgated what he calls the *monhormonic theory* of sexual differentiation for mammals. He has postulated that only the male hormone plays a rôle in sexual differentiation. Sexual differentiation takes place in the female in the normal manner because no male hormone is present and female differentiation according to this theory is therefore anhormonic. Sexual differentiation takes place in the male in the normal manner because male hormone is present to cause such development. The female hormone has no influence on sexual development. The essential non-validity of this postulate will be demonstrated later.

Dantchakoff [10-14] presented the first evidence that the male hormone is capable of masculinizing the embryonic mammal. She injected the male hormone directly into the amniotic cavity of 15-day embryonic guinea pigs and noted that a marked masculinization of the female embryos resulted.

Working without knowledge of Dantchakoff's discovery, we also obtained evidence that male hormones could markedly influence embryonic sexual development.[15-17] Our method differed from Dantchakoff's in that the hormones were administered to the pregnant female. To date 256 pregnant rats have been injected with various androgens. Testosterone, which is presumably the true male hormone as found in the testes, was the first substance used. Other androgens used were: testosterone propionate, androsterone, dehydroandrosterone and androstenedione. One hundred eighteen of these injected pregnant rats have carried their pregnancies to term. The male offspring of these litters have been essentially normal, but the female offspring have been markedly masculinized. Two hundred fourteen intersexed or masculinized female rats have been obtained and examined either as newborn or as adults. Well modified animals resemble the male in that no external vagina is present and the phallus is a penis instead of a clitoris. Internally these animals have organs of both sexes. Oviducts, uteri and upper vagina are present combined with epididymides, ejaculatory ducts, the various prostatic lobes, a male urethra and Cowper's glands. The portion of the upper vagina which is present communicates with the urethra at the level of the normal uterus masculinis. No lower vagina is present.

Raynaud,[18, 20] using our method, subsequently confirmed these findings in the mouse. A definite effect of the male hormone on sexual development has been demonstrated, then, in three different mammals, the guinea pig, the rat and the mouse.

In theory, a similar demonstration of the opposite effect, i.e., the effect of female sex hormone on sexual development, would be impossible. The administration of estrogenic substances to the pregnant animal has been claimed by various workers to interfere with pregnancy either by causing abortion or by causing fetal deaths and resorptions of the pregnancies. However, we have administered large doses of various estrogens to 212 pregnant rats. One hundred of these animals have carried their pregnancies to term. The estrogens which have been used are: estradiol, the probable true ovarian follicular hormone; and estradiol dipropionate, a doubly esterified form having a more prolonged effect than estradiol. As a result of this treatment, a marked feminization of the genetic male offspring has been obtained. One hundred and twenty-five of these intersexed or feminized male rats have been examined to date. Typically female structures, such as nipples, vagina and portions of the uteri and oviducts, are found. In addition, there is a marked inhibition in the development of male structures. Prostates are not present. Seminal vesicles are very small and may not be grossly visible in the adult. The vasa deferentia and epididymides are

partly or almost completely absent. The gonads are in a position typical for the female rat, i.e., at the base of the kidneys. The external genitalia are also feminized in that the phallus is small and hypospadiac with the vagina and urethra having a common opening at its base.

These experimental results show that the sexual development of the genetic female may be modified in the male direction by male sex hormone and that the sexual development of the genetic male may be modified in the female direction by female sex hormone. These results therefore lend credence to the dihormonic theory and apparently disprove Wiesner's postulated monhormonic theory inasmuch as the female hormone has been shown to have a profound effect on the sexual development of the genetic male.

The dihormonic theory is generally interpreted to mean that sexual development in the male is solely under the control of male hormone produced in the embryonic testes and that development of the female is solely under the control of female hormone produced in the embryonic ovaries. The male hormone, then, causes the Müllerian duct to degenerate and causes the Wolffian duct to develop into epididymis, vas deferens, etc., and the urogenital sinus to form prostates, etc. The female hormone causes the Wolffian duct to degenerate and causes the Müllerian duct to develop into oviducts, uteri and upper vagina and the urogenital sinus to develop into lower vagina and female urethra.

Further analysis shows that our experimental findings do not entirely fit into this theory. The estrogens produce effects in accordance with their postulated functions in that they cause inhibition of the Wolffian duct, stimulation of the Müllerian duct and influence the urogenital sinus to develop in the female direction. The androgens, however, do not fully cooperate with the theory inasmuch as they cause stimulation of the Wolffian duct and modification of the urogenital sinus in the male direction, but have never shown any definite evidence of inhibiting Müllerian duct development. In the masculinized females, oviducts, uteri and upper or Müllerian vagina are present intact.

The fact that part of our experimental findings do not entirely fit the theory does not necessarily destroy its essential validity. Perhaps the male hormones we have used are not identical in action with the embryonic male hormone, or perhaps the matter is quantitative, i.e., the administered androgen does not reach the embryo at the proper stage of development in sufficient quantity to inhibit Müllerian duct development.

However, further study of our experimental material has led to some very disturbing and, at present, somewhat inexplicable findings. Twenty newborn genetic female offspring of mothers which received various dosages of estrogens have been serially sectioned. In 19 of these animals definite evidence of masculinization has been found. Wolffian duct derivatives, the vasa deferentia and ejaculatory ducts, have been found in various stages of preservation. In addition there is some inhibition of female structures.

The ovarian capsule, which is normally present in the female, is lacking, and development of the urogenital portion of the vagina is inhibited. Inspection of the gonad is required usually to distinguish between the genetic males and the genetic females (figures 2A and B).

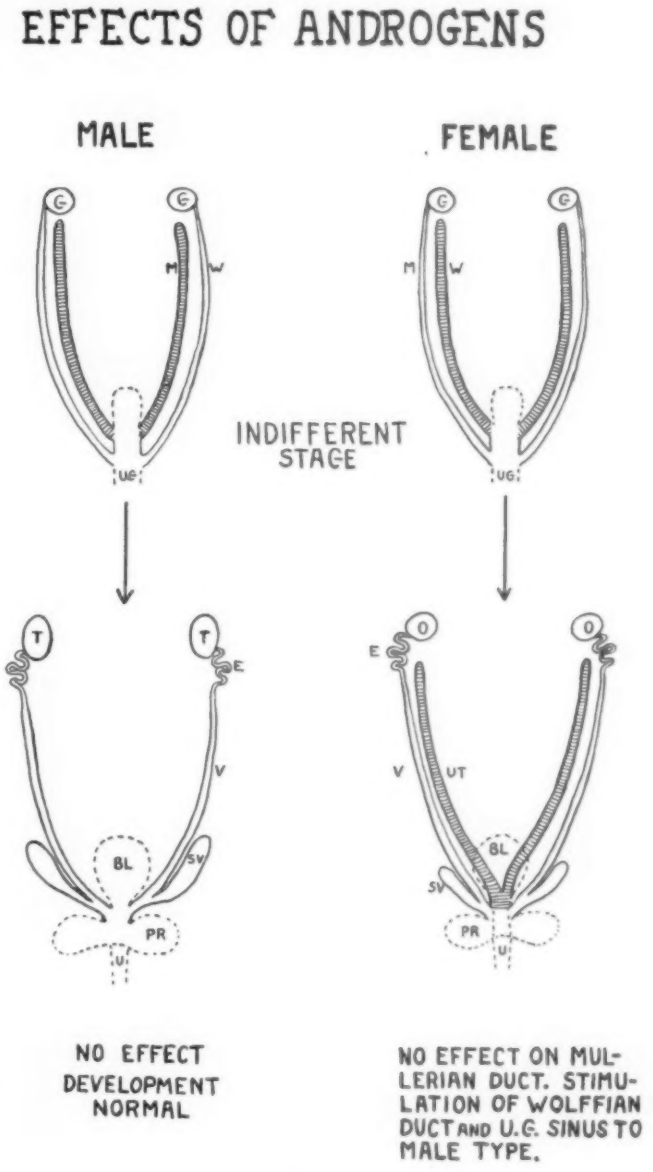

FIG. 2A.

Thus we have an apparent paradox. Administration of estrogens in large amounts to pregnant rats has caused " feminization " of the genetic male offspring and " masculinization " of the genetic female offspring.

It must be remembered, however, that these hormones have been administered to the pregnant rat. We are not justified in concluding that this masculinization of the female embryo is due to a *direct* action of the estrogen

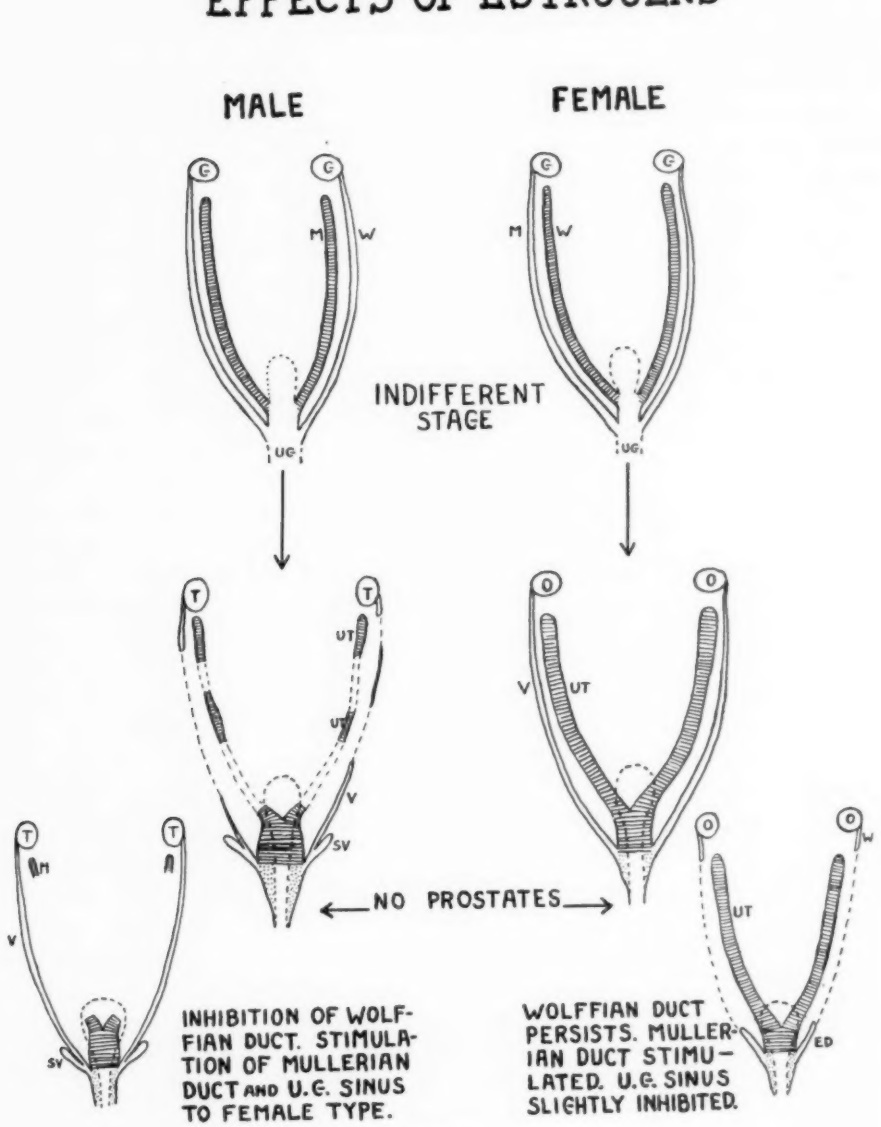

FIG. 2B.

on the embryo. The possibility that this effect is secondary in nature cannot be dismissed. It is well known that androgens are normally present in the female. Androgens have been extracted from ovaries,[21] from adrenals [22]

and from placentae,[23] but exactly where these androgens are produced is not known. Progesterone, the hormone of the normal corpus luteum, is also known to be androgenic.[24] Before it can be concluded that the estrogens administered to the pregnant rat have directly masculinized the female embryos in utero, a further possibility must be ruled out. The physiological mechanisms of the body are well balanced. In all probability the hormones of the pregnant organism (androgens plus estrogens) have little or no influence on the development of the embryo. When very large amounts of estrogens are introduced into the pregnant rat, perhaps the body, in an attempt to return the hormone balance to normal, causes a production of sufficient androgen to masculinize the female embryo. This explanation, however, is obviously inconsistent. If in response to administered estrogens, the pregnant rat produces sufficient androgen to masculinize the female embryo, one would expect the androgen so produced to counterbalance also the effects of the administered estrogens on the male embryo so that no feminization of the male should result.

In the case of the apparent paradoxical effects of estrogen, one has to consider the possibility that the relatively large doses suppressed the gonads either directly or indirectly via the anterior lobe. The entire matter is rather complicated and there is no immediate need to present an explanatory theory or hypothesis, which can be readily done. However, we shall await the accumulation of further experimental facts before exposing any new theory. It is sufficient for the present to state that the existing theories are in part inadequate and that sexual differentiation or development of a male or female mammalian embryo may be modified by the sex hormones.

Clinical Application

During the present century there have been numerous articles, monographs and books written about intersexuality in the human. Theories as to the mechanisms of production of these anomalies are almost as numerous as are the articles. No attempt will be made to review these articles or theories. However, an attempt will be made to explain some forms of human intersexuality on the basis of the knowledge gained from the study of experimentally produced intersexuality in mammals.

The occurrence of some forms of intersexuality in the human is much more common than is generally realized. Hugh Young has stated that pseudohermaphroditism occurs in one individual out of 1,000. It has been our privilege to observe three cases of pseudohermaphroditism in the human. Two of these cases were probably genetic females and one a genetic male. The findings in these individuals greatly resemble those in our experimental animals.

The two genetic females have previously been reported by Dr. H. O. Jones [25] and by Dr. W. T. Carlisle.[26] Both of these children externally resembled males in that a hypospadiac penis-like organ was present, while

no vagina was visible. Laparotomy revealed the presence of apparently normal ovaries, fallopian tubes, uterus and upper or Müllerian vagina. On cystoscopic examination (by Dr. Harry Culver) it was found that the vagina emptied into the urethra about 1 cm. below the bladder neck. Conditions identical with these have been found in some of our less well modified masculinized female rats obtained when androgen was administered late in the developmental period.

It is known that sexual differentiation of the external genitalia takes place relatively late in embryonic development. Apparently, in the female cases cited, an abnormal concentration of androgen affected development after the Wolffian ducts had already normally regressed but while the urogenital sinus and genital tubercle were still in a plastic stage so that they were influenced to develop in the male direction, consequently no lower

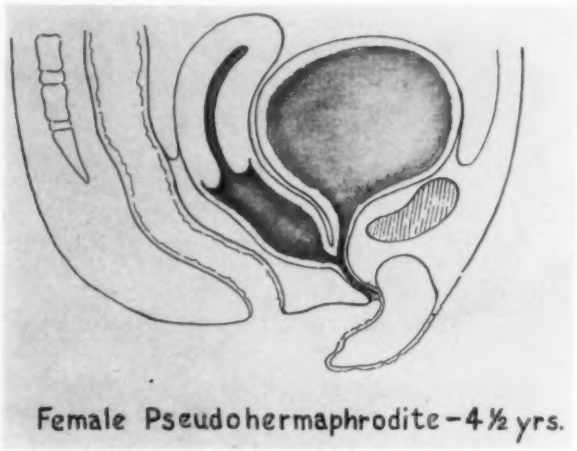

FIG. 3.

vagina is formed and a male type of phallus is developed. The upper or Müllerian vagina is left in communication with the urethra at the same level where, in the embryo, the Müllerian ducts communicate with the urogenital sinus (figure 3).

Externally the human male pseudohermaphrodite resembled a female, having a clitoris, large labia majora, labia minora, a vaginal introitus and female urethra. In the left labium majorum, however, a small testis with its epididymis was palpable. Another testis was palpable in the right groin. Laparotomy by Dr. Harry Culver revealed no evidence of a uterus nor of oviducts. This individual was 19 years old and had the habitus and hirsutes of a normal male.

In this individual an abnormal concentration of estrogen during embryonic development may have been the cause of the intersexed condition. An excessive amount of estrogen may have been present after degeneration of the Müllerian ducts had occurred, but before sexual differentia-

tion of the urogenital sinus and genital tubercle had taken place. These latter structures, being still in a plastic state, responded by developing in the female manner (figure 4).

Other cases presented in the literature may be explained in a similar manner. In some of these individuals hormonic influences apparently have been effective earlier in embryonic development and greater changes have resulted. Young [27] and Von Neugebauer [28] mention prostates in masculinized females. Young describes two cases of almost completely feminized males with testes, oviducts, uterus and vagina. Only one of these had any traces of Wolffian duct derivatives (vasa deferentia). In these individuals, if the conditions were hormonal in origin, abnormal concentrations of

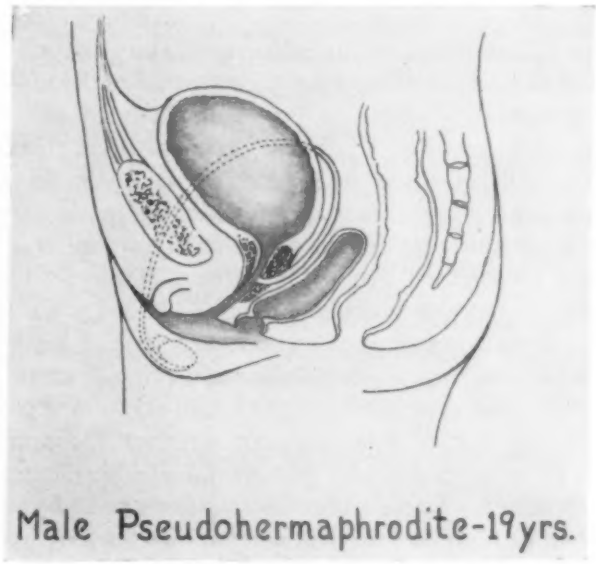

FIG. 4.

estrogens must have affected development in the very early plastic state, too late to influence differentiation of the gonads, but early enough to inhibit the Wolffian duct and stimulate the Müllerian duct and to cause female differentiation of the urogenital sinus.

We do not intend to imply that all cases of intersexuality in the human are due to hormonal conditions. It is quite probable that some of these abnormalities are directly due to genic factors. We also do not intend to enter into the discussion as to the sources of the hormones which may cause these abnormal sexual changes. Some may arise from abnormalities in the maternal organism. It has also been theorized that androgens produced by the abnormal fetal adrenals may be the causative agents in the production of masculinized female intersexes. In support of this theory is the fact that androgen producing adrenal hyperplasia or adenoma have been reported in masculinized females.

Sex Behavior

Since some psychiatrists believe that true sexual inversion, or homosexuality, is a congenital defect, many physicians have inquired about the sexual behavior of our intersexed rats. We can only say that our observations to date indicate that the definitely intersexed rats are " neutral " in that they respond neither as males nor as females. This neutral sexual behavior is like that of a gonadectomized rat some time after gonadectomy. This subject is one, however, in which the use of special technics or approaches is required to provide accurate data. We hope in the near future to make a scientific study of the problem.

It should be pointed out that the problem is capable of solution by scientific methods. The question is: Is true homosexuality a congenital defect that results from a sex hormone disturbance? The answer to that question depends on the answer to the following question: Does the male sex hormone prenatally or prepuberally organize in the brain a specific male behavior pattern? The same question, of course, applies to the female. We now know that the sexual activity of the castrated *mature male rat* is increased above the castration level by the daily injection of *female hormone*.[29] This shows that the male hormone does not specifically organize the male mating (copulatory and ejaculatory) behavior pattern in the adult male rat, but merely activates a pattern already present. The female hormone may arouse the male by causing congestion or tumescence of his genitalia. But, we do not know whether the adult male learned prior to castration to behave as a male, so that when estrogen was given him the tumescence of his genitalia caused him to act as formerly; or, whether his brain in utero or prepuberally was so organized by his own male hormone that he could behave only as a male? These and other questions must be answered before we can say whether homosexuality is congenitally acquired on the basis of a sex hormone disturbance. Of course, we know that sex hormones activate the sex urge, but we do not know that they specifically direct the urge in a male or female direction.[30] If it is found that sex hormones do not specifically organize sexual behavior in the rat, certainly they will not do so in man where environmental and psychological factors play such a prominent rôle. However, it must be remembered that a neuter-sexual person—a lack of both hormones or an anatomic pseudohermaphrodism—may be more readily directed in either the male or female direction of behavior by environmental conditions than a non-neuter-sexual person.

Summary

Conclusive experimental evidence is now available showing that the sex hormones have a profound effect on the intrauterine sexual development in mammals.

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OBESITY AND HYPERTENSION: CLINICAL AND EXPERIMENTAL OBSERVATIONS *

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Clinical studies have indicated a definite correlation between obesity and increased systolic blood pressure. This observation has received statistical support from several angles. There is also a general impression among physicians that overweight unfavorably influences an existing essential hypertension, while often but not always blood pressure levels fall with weight reduction. Aside from these generalizations little can be learned from the literature relative to any specific or prolonged effects of weight reduction on hypertension. True enough, several small recorded series indicate blood pressure fall with weight reduction but we have found no long time experiments to indicate the contrary side of the question; namely, the effect of a rapid weight gain on blood pressure. Consequently we have attempted to study hypertensive and non-hypertensive dogs whose weight could be varied by the amount and kind of food intake. It is, therefore, the primary purpose of this paper to state briefly the effect of obesity on the systolic and diastolic pressures of dogs and, if possible, to draw any clinical application that might arise—an interesting but often misleading pastime.

Before going into the experimental side of the problem it seems advisable to note that a fairly strong correlation can be built up between obesity and hypertension along three general lines: First, statistical studies have been made on several large series of individuals who in the main can be considered normal. For example, in over 500,000 insured men [1] there was a definite rise of both systolic and diastolic pressure with increasing weight. Fortunately, in this study the age factor was carefully considered, and increasing weight still held as a definite correlation with rising blood pressure for all age groups. From a study of 5,364 white prisoners, Alvarez and Stanley [2] have concluded that after the age of 35 fatness tends to increase systolic blood pressure and thinness tends to decrease it. Fatness and leanness have a slight effect on diastolic pressure. Huber [3] finds only slight statistical significance to a direct correlation between increased weight and increased systolic blood pressure in a study of 1,332 healthy men. Dunham [4] likewise relates overweight and blood pressure elevation but indicates a closer association between variation in blood pressure and age than between variation in blood pressure and body weight.

A second and somewhat more exciting approach has been the clinical study of obesity and hypertension. Master and Oppenheimer [5] reduced 53 obese patients with essential hypertension an average of 25 to 30 pounds

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and observed an average fall of 25 to 30 mm. Hg in systolic blood pressure and 15 to 20 mm. Hg fall in the diastolic. It is not clear how long the pressure stayed down or its eventual course.

Symonds,[6] in an analysis of 150,419 policy holders in the Mutual Life Insurance Company, found that systolic and diastolic blood pressure increased with both age and weight. These individuals were divided into 10 groups, four of which varied from 5 to 35 per cent below normal weight; a normal group, including those from 5 per cent below to 5 per cent above ideal weight; and five groups weighing from 5 per cent to 50 per cent more than normal. The blood pressures of these ten weight groups were tabulated according to age at intervals of five years from 15 to 60 years of age and over. Though there appeared a constant rise in blood pressure with both increasing age and weight the differences were small, the average blood pressure at age 40 to 44, for example, being 119 mm. Hg systolic and 79 diastolic for the group 35 per cent underweight; 126/83 mm. Hg for the normal group; and 133/89 mm. Hg for those who were 50 per cent overweight.

Dublin, Fiske, and Kopf [7] in reviewing the results of periodic health examinations in 16,662 policy holders of the Metropolitan Life Insurance Company, found 20 per cent of these individuals to be overweight. Among this group 12.8 per cent showed elevations of blood pressure from 20 to 40 mm. Hg above normal. Only 2.5 per cent of the remaining number showed equally high blood pressure. These authors conclude that obesity and elevated blood pressure are very closely related.

Perhaps more closely approaching the question of relationship of pathological changes in blood pressure and body weight are the studies of consecutive patients admitted to hospitals and clinics, such as those of Hartman and Ghrist [8] who studied the relationship of body weight to blood pressure in 2,042 consecutive registrants at the Mayo Clinic. In six groups of patients, varying from 50 per cent underweight to 75 per cent overweight, there was found to exist an almost step-like increase of systolic blood pressure from groups one to six. The diastolic pressure did not show such consistent changes. Therefore, weight was thought to be a dominant factor in determining systolic blood pressure.

Palmer [9] finds obesity three times as often in 100 unselected cases of hypertension as in 100 unselected ward patients suffering from miscellaneous diseases.

The common occurrence of a fall in blood pressure in obese patients with hypertension who voluntarily lose an appreciable amount of weight is a well known fact. Bearing directly upon this question are the striking observations of Terry,[10] made upon 63 obese female patients who showed an average blood pressure of 173/96 mm. Hg. The average weight of the individuals in this group was 199½ lbs. Though none of them showed any clinical symptoms of renal damage, 58 per cent were found to have definite hypertension. The average blood pressure of 24 members of this latter

group who were studied while on a reducing diet fell from 196/103 mm. Hg to 170/95 mm. Hg. The greatest loss of weight was 60 pounds in a period of 14 months. In this instance the blood pressure changed from 190/90 mm. Hg to 148/95 mm. Hg.

Still a third approach is somewhat more indirect but may have bearing on the subject. Randall [10] noted the average gain in weight for primigravid women and found this to be 33 pounds for those who became victims of the late hypertensive toxemia of pregnancy, whereas the non-toxemic patients gained 22 pounds. From the records of the University of Virginia Hospital it appears that following the late hypertensive toxemia of pregnancy obese women are nine times as likely to develop residual hypertension as those who remain normal or near normal weight.

In brief, although a correlation apparently exists between overweight and elevated systolic pressure it cannot be said that obesity is a cause of essential hypertension. Many obese people have low blood pressure, whereas many thin persons have hypertension. However, if this association of overweight and hypertension does exist, obesity should be studied as a secondary factor sometimes precipitating a pressor mechanism.

For the past five years we have been making observations of the blood pressure of both normal dogs and dogs with experimentally produced hypertension. Lasting elevation of both systolic and diastolic pressure has been produced in these animals by three different methods: namely, excision of renal tissue, ligation of renal arteries, and partial obstruction to blood flow through the kidneys by application of Goldblatt clamps [11] to the renal arteries. The latter method has generally resulted in higher elevation of blood pressure for a longer period of time than have the other two procedures.

The blood pressure has been recorded by the method first introduced for unanesthetized dogs by Kolls,[12, 13] in which the Erlanger [14] method of recording human systolic and diastolic blood pressure has been adapted to this use. For a detailed description of this apparatus and method the reader is referred to a recent paper by the present authors [15] in which a diagram appears indicating the several minor but advantageous changes in setting up the apparatus.

Our animals have been fed upon several brands of prepared dog food, each containing less than 20 per cent protein, to which have been added cod liver and raw beef at frequent intervals. Almost all of them have remained well nourished and otherwise apparently in healthy condition though, due to lack of space for out-door runways, it has been necessary for the dogs to remain in cages throughout the experiment. Thus, though far from a natural environment, their living conditions have been pretty well standardized.

Our present study began as the result of observations made upon one of the dogs of this group (figure 1; Dog C–34) to whose renal arteries Goldblatt clamps had been applied five months previously. This dog, whose

weight had fallen from 44 to 33.5 pounds, regained this loss within one month when fed three pounds of raw beef daily and, for the following three weeks, continued to gain weight on his regular diet without the beef. During this period both systolic and diastolic blood pressure, which had remained elevated throughout the period of poor nutrition, rose sharply to even greater heights but gradually fell to average post-operative levels when the

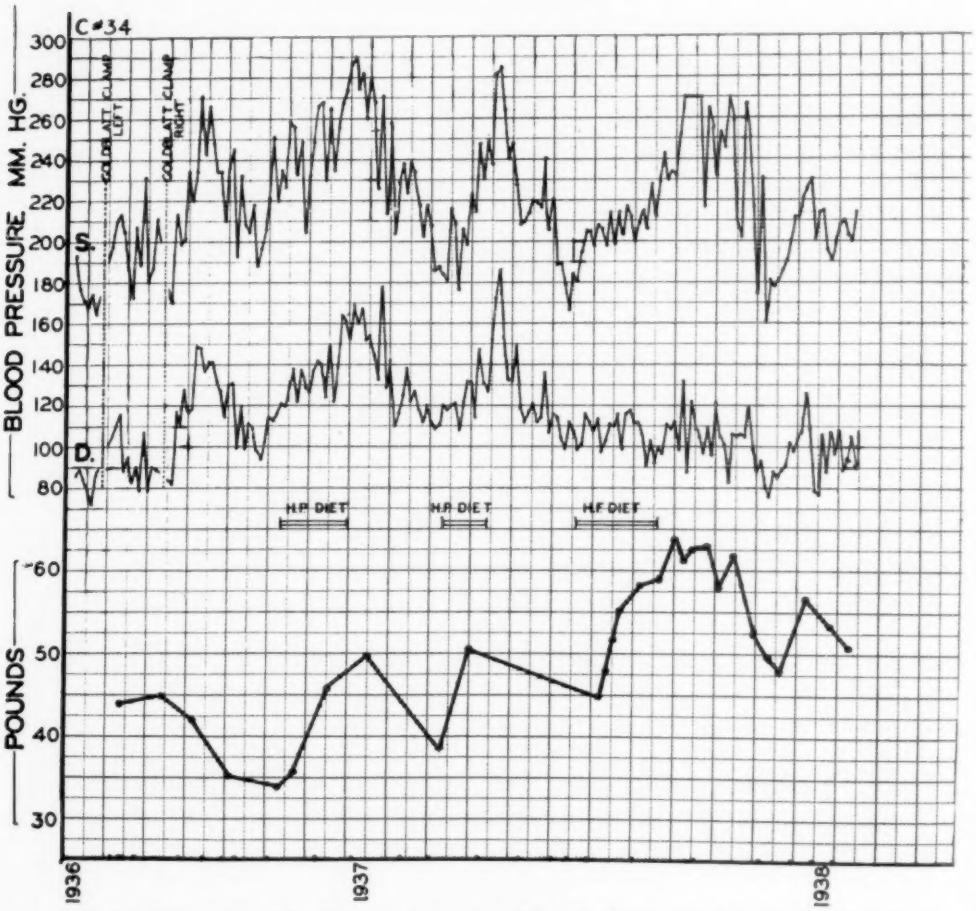

FIG. 1. Dog C No. 34: Mean systolic and diastolic blood pressure as related to body weight during all lean meat (H. P.) diet and standard plus high fat (H. F.) diet. Dog fed on standard diet during unmarked period.

meat was withdrawn from the diet. After an interval of two months, during which time the dog received the regular diet and lost approximately 9.5 pounds in weight, the blood pressure remained within the elevated range usually seen after constriction of the renal arteries. At this point the all meat diet was resumed. The prompt gain in weight of 12 pounds which followed was again accompanied by marked rises of both systolic and diastolic pressure.

During the course of this experiment two other dogs were placed upon a less abundant, all meat diet. One of these dogs had bilateral Goldblatt clamps, the other partial nephrectomy. These animals were well nourished at the beginning of the experiment and were given only one and one-fourth pounds of lean beef daily, an amount thought to be adequate for the maintenance of body weight but not sufficient to cause much gain. This was done for the purpose of determining whether or not an all meat diet would cause a rise in blood pressure in dogs who did not gain weight. The weight of neither animal changed materially during this time, nor did there occur any appreciable changes in blood pressure.

The result of this experiment suggested strongly that the increase in weight rather than the all meat diet was the factor more closely associated with the rise in blood pressure observed in Dog C–34 (figure 1). It then seemed desirable to us, before pursuing further the complicated question of the effect of proteins upon blood pressure to ascertain whether such rises in blood pressure followed increase of body weight produced by other types of diet. Accordingly, four normal dogs and four dogs with longstanding experimental hypertension were fed for one month mainly upon beef fat (table 1). Each of these animals received daily one pound of ground beef fat mixed with about a half pound of the usual standard dog food. Dogs quickly regurgitate large amounts of fat eaten alone but retain and ap-

TABLE I

BLOOD PRESSURE CHANGES RELATED TO CHANGE IN BODY WEIGHT IN EIGHT DOGS

DOG #	WEIGHT			BLOOD PRESSURE						WT. GAIN	B.P. CHANGE		WT. LOSS	B.P. CHANGE	
	LEAN	FAT	LEAN	LEAN		FAT		LEAN							
				S.	D.	S.	D.	S.	D.	(LBS)	S.	D	(LBS)	S.	D.
31	39	50	41	216	106	252	98	171	85	11	+36	-8	9	-81	-13
34	45	63	49	196	106	245	109	177	85	18	+49	+3	14	-68	-24
3	33	44	36	176	92	214	85	169	83	11	+38	-7	8	-45	- 2
2	28	33	28	153	84	156	79	153	81	5	+ 3	-5	5	- 3	+ 2
33	35	51	44	123	67	172	68	131	57	16	+ 49	+1	7	-41	-11
16	31	36	31	166	78	224	84	179	65	5	+ 53	+6	5	- 46	-19
35	35	51	43	158	82	185	83	168	82	16	+ 27	+1	8	- 17	- 1
30	30	41	31	152	69	167	71	132	54	11	+ 15	+2	10	- 35	-17

Mean systolic and diastolic blood pressure before, during, and after weight gain for each dog. Dogs C No. 34 and C No. 31, hypertension produced by Goldblatt clamps. Dogs C No. 3 and C No. 2 hypertension produced by reduction of kidney tissue. Dogs C No. 33, C No. 16, C No. 35 and C No. 30 not subjected to any operative procedure; apparently normal dogs.

parently relish the mixture which these animals were given. After receiving this diet for a month, the dogs were again given their regular food in amounts varying from one-half to one pound daily, an attempt being made to regulate the food of each animal in such a manner that the weight would slowly decrease. It will be seen that we had considerable difficulty in accomplishing this end in several animals.

The results of this experiment are recorded in table 1. Dog C–2 (figure 2), whose right renal artery and two of three main branches of the left renal

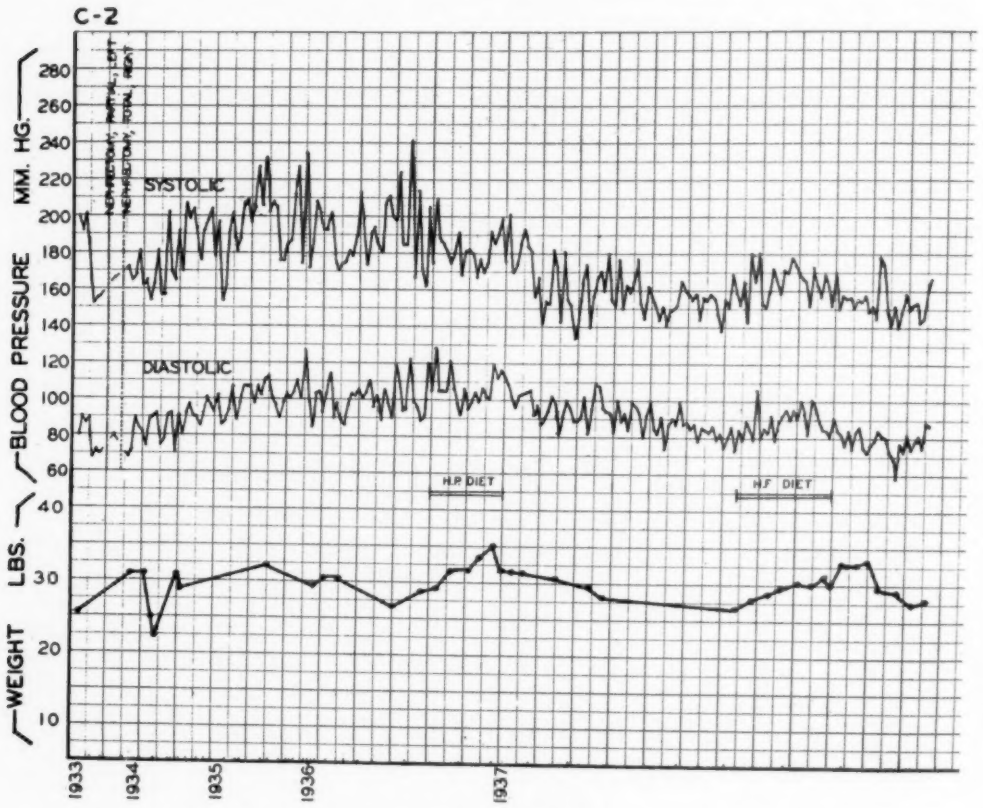

FIG. 2. Dog C No. 2: H. P. = High Protein Diet. H. F. = High Fat Diet.

artery were ligated in December 1933, has never varied much in weight during four years of observation. This animal did not gain appreciably on the high fat diet nor was there any significant change in either systolic or diastolic blood pressure during this period. All of the other seven dogs were well nourished at the beginning of the experiment and quite obese at the end. Each of them showed a marked rise of systolic blood pressure, often exceeding 280 mm. Hg, the highest pressure which we can record consistently with our apparatus. As the weights of the dogs decreased, systolic blood pressure returned to its original level in each case. No ap-

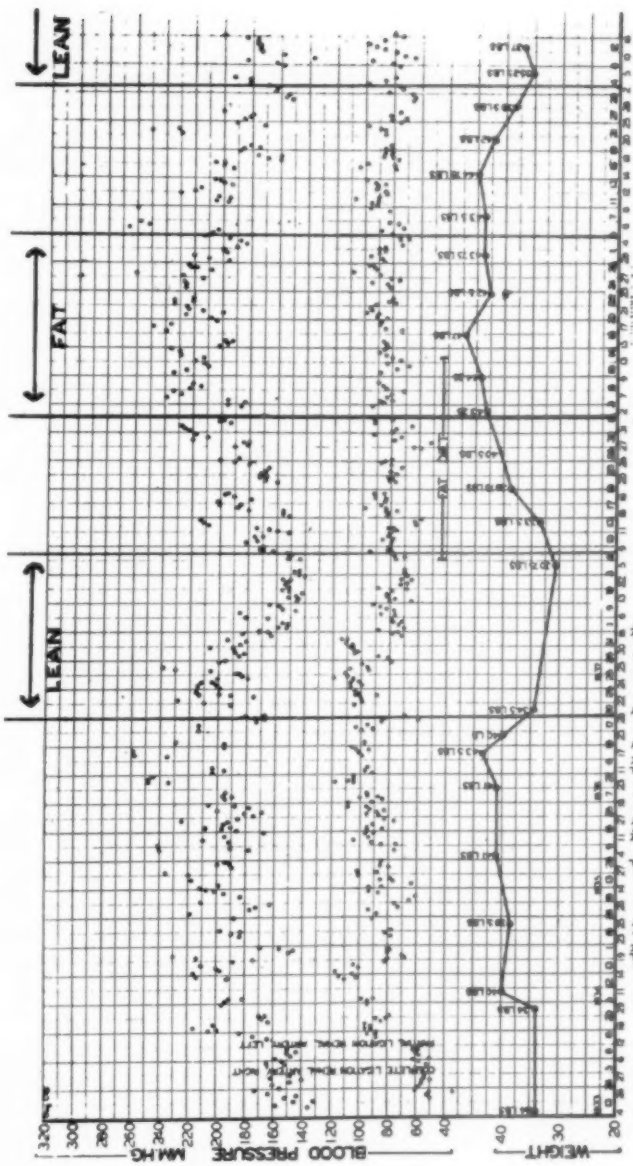

FIG. 3. Dog C No. 3: Individual systolic and diastolic blood pressures recorded in this dog to indicate method by which the mean figures before, during and after weight rise were obtained for table 1.

preciable rise of diastolic blood pressure occurred in any of these animals throughout the experiment, but an appreciable fall in diastolic pressure occurred in five of the eight animals following a sharp loss of weight.

Table 1 presents a summary of the effects of weight change in four hypertensive and four non-hypertensive dogs. In each instance the mean systolic and diastolic pressure has been determined over a period of a month or more prior to, during maximum weight gain, and after the animal has been reduced by food restriction to approximately the original weight level. In every instance except one a sharp rise of 15 to 53 mm. Hg systolic blood pressure occurred with a definite increase in weight. The one exception serves as an additional control observation. This animal (Dog C–2; figure 2), a large bony german shepherd, gained only five pounds, an insignificant weight gain for original size, and no change occurred in blood pressure level. Dog C–16, a small nervous mixed breed female, was quite well nourished at 31 pounds and a weight gain of five pounds made this animal quite fat with a sharp rise in systolic pressure. Equally as striking is the systolic pressure fall with weight loss. This frequently proved to be greater than the original rise. Little diastolic change occurred with the weight rise but with weight reduction diastolic pressure fell below its pre-diet level in five of the eight animals. It is not clear at present whether this recorded fact is of significance. These mean figures may be verified and studied in detail from the records of a previous publication.[16]

There is one criticism concerning the accuracy of the systolic blood pressure recorded in these experiments which we wish to mention at this time. It has been the common experience of all workers employing the apparatus which we have used that the cuff must be well fitted and placed as high as possible on the thigh to assure obliteration of the femoral artery. The possibility therefore exists that the increase in size of the leg which accompanies marked gain in weight might interfere to some extent with the compression of the underlying artery, thereby causing the systolic pressure only to appear to be elevated. It is possible that an error of from 5 to 10 mm. Hg might be due to this, but we do not think that such marked and consistent apparent elevations of systolic pressure could be accounted for in this manner. Our main basis for this belief is the consistency with which the systolic pressure rose apparently independently of the actual amount of weight gained.

In these experiments we have been careful to throw out all sphygmographic records in which systolic pressure was doubtful. That observations are accurate at widely separated weight levels is shown by the recorded curves on Dog C–34 where the systolic as well as diastolic pressure at 45 to 50 pounds is even higher than the pressure for 62 to 64 pounds weight. Again, in animal C–30 there is a sharp rise in weight, twelve pounds, with only a slight or moderate rise in systolic pressure. Previously published curves [16] illustrating this method have suitably demonstrated wide variations in blood pressure at constant weights. Furthermore, maximum-minimum

valve studies to check the accuracy of the method have been reported.[13] However, owing to the violent changes in weight the systolic observations should be checked by another method to establish the rather striking results reported here.

Discussion

From these experiments it seems clear that both normal dogs and dogs with experimental hypertension produced by two different methods show marked increase of systolic blood pressure when caused to gain large amounts of weight by feeding them a diet composed chiefly of beef fat. Though the final explanation of this rise in blood pressure is not known, it seems most likely that it is intimately associated with the increase of body weight. This assumption is further supported by the fact that two dogs, whose weight was maintained by feeding raw beef only, showed no change in blood pressure, while one dog, fed entirely on raw beef in amount sufficient to cause marked gain in weight, developed marked elevation of both systolic and diastolic pressure. Though it is of considerable added interest that the diastolic pressure of this latter animal showed such a marked rise during the period of excessively abundant high protein diet, our studies of the experimental conditions to which this dog was subjected are not yet adequate to justify further comment.

It has been of much interest to us that both groups of dogs, hypertensive and normal, gaining weight on a high fat diet have shown a rise of systolic pressure only. This observation suggests that the hypertension of obesity is in some way fundamentally different from the hypertension experimentally produced by interference with blood flow through the kidneys, under which condition the diastolic as well as the systolic pressure is always elevated.

Weight reduction in patients has been followed by a fall in blood pressure and symptomatic improvement. Although this particular phase of the discussion does not fall within the scope of this paper we are not unmindful of the fact that improvement following weight reduction is not based on systolic blood pressure fall wholly, but mainly upon mechanical and chemical factors, particularly a reduction of cardiac work for exercise.[17]

This similarity in behavior of systolic blood pressure relative to body weight in dog and man does not imply a causal relationship between obesity and essential vascular hypertension. Furthermore, the rapidity of forced weight gain and weight loss in these dogs partially invalidates any careful comparison with clinical experience. The true relationship of obesity to human hypertension remains to be shown, but an explanation previously suggested,[18] that obesity may act mechanically to produce increased resistance in the peripheral vascular stream bed, seems most likely.

Conclusions

The literature indicates a definite association between obesity and systolic blood pressure elevation in a fair number of instances.

Systolic blood pressure in normal and hypertensive dogs rises with weight gain and falls with weight loss, while diastolic pressure varies little.

These observations do not indicate that obesity is a cause of essential hypertension but support the idea that overweight may be a factor of importance in the elevation of systolic blood pressure.

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THE INFLUENCE OF IRON AND DIET ON THE BLOOD IN PREGNANCY *

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True anemia of pregnancy may be defined as a condition characterized by decrease in red blood cells or hemoglobin or both below the levels which may be considered as physiologic for the period of gestation, such decrease being associated with and dependent upon the gravid state. It is to be distinguished from anemia coincidental with pregnancy such as may result from hemorrhage, infection or primary blood dyscrasia.

The significance of anemia of pregnancy lies in its prevalence, its effect upon the health of both mother and infant, its response to appropriate therapy and its preventability. Moreover, accurate blood examination as part of prenatal care derives its importance not only from the direct effects of such anemia as may be disclosed, but also from the possible evidence of deranged metabolic processes, which are often reflected by relatively slight deviations from the normal blood values.

The present communication deals with blood and dietary studies carried out on 158 pregnant women. Of these, observations on 133 were sufficiently frequent, including examinations made six weeks after delivery, and treatment sufficiently well carried out, to permit satisfactory evaluation of therapeutic measures. The subjects, attending the out-patient maternity service of the University Hospital, represent a fair cross-section of medium and low income groups. Most of them were residents in small urban communities and about 40 per cent received welfare assistance. The majority of the patients were in their early twenties but the range of ages was wide. Approximately two-thirds had had one or more children, and there was no evident relationship between parity and the incidence or severity of anemia.

Ninety-six members of the group were interviewed by a dietitian with the object of ascertaining dietary habits and their conditioning factors, and of correcting such habits where indicated in accordance with the special requirements of pregnancy and the ability of the patient to secure foods recommended. Subsequent consultations were held for the purpose of determining adherence to instructions and for further advice and adaptation of the diet to changing clinical conditions. The basic diet recommended for pregnancy is that formulated by the League of Nations Technical Commission.[1] It provides, in addition to other so-called protective foods in quantities considered adequate, a daily protein intake of approxi-

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mately 80 grams of which about 50 grams are supplied by meat, eggs, milk and milk products. Adequacy of vitamin B_1 (thiamin) has been set at an approximate minimum level of 15 units per 100 calories [2] and of riboflavin at a minimum level of about 500 units daily.[3] The intake of nicotinic acid has been considered to parallel that of riboflavin.

All blood examinations were made on oxalated venous blood in accordance with a standard procedure previously described.[4] Erythrocyte counts, hemoglobin estimations and packed cell volume hematocrit determinations were made, after the first ante-natal examination, at monthly intervals, whenever possible, throughout the remainder of the pregnancy, during labor, 10 days after delivery and 42 days after delivery.

The recognition and classification of anemia in association with any physiologic state, such as pregnancy, requires the preliminary establishment of standards of normality for that state. No wholly satisfactory standards for the blood values in pregnancy have as yet been formulated and among investigators there is considerable divergence of opinion regarding the minimum levels of the red blood cell count, hemoglobin and packed cell volume which may be considered normal for the pregnant woman. The increase in plasma volume which commonly accompanies gestation results in a diminished concentration of the corpuscular elements of the blood,[5] and whereas this is usually more than compensated for in the case of the leukocytes, an increase of the red blood cells corresponding to that of the plasma commonly fails to occur. Assumed minimum levels for pregnancy based on the observed maximum degree of plasma dilution and the lower limit of the normal range for non-pregnant women are open to a number of objections, including the lack of knowledge in the majority of individual cases of either the pre-gravid blood level or the actual increase of plasma volume. Values that, in pregnancy, may be physiologic for one woman for another may indicate a pathologic trend. Tentative standards for average and minimum red blood cell and hemoglobin values in pregnancy have been determined on our subjects on the basis of evidence of return, within six weeks after delivery to non-pregnant normal levels, in the absence of medicinal or diet therapy. The detailed data from which these standard values are derived will be reported elsewhere. In brief, we regard an erythrocyte count of less than 3,500,000 per cubic millimeter or a hemoglobin value of less than 10.0 grams per 100 c.c. occurring at any time during pregnancy as evidence of true anemia (table 1).

The majority of instances of anemia of pregnancy appear to fall in the iron deficiency group. Yet normal gestation places no great demand upon maternal iron stores.[6] The total additional requirement of iron incident to pregnancy does not exceed 250 milligrams or approximately the amount contained in 500 c.c. of blood. Consequently the high incidence of iron deficiency anemia among pregnant women indicates four possible etiologic factors: (1) prevalence of low iron reserves among non-pregnant women; (2) restricted utilization of reserve iron in satisfying maternal iron re-

quirements; (3) impaired absorption of dietary iron during gestation; (4) low intake of food iron. The two last mentioned conditions can hardly operate as sole or major causes of anemia during pregnancy.

It has been common experience that a considerable percentage of cases of anemia associated with pregnancy fail to respond satisfactorily to iron therapy. In previous reports of clinical [4] and experimental [7] studies evidence has been presented that such anemia is dependent upon deficiencies of the diet, and that it may be differentiated from iron deficiency anemia by

TABLE I

Tentative Standards of Normality for the Blood in Pregnancy

Average Normal Blood Values

	Month of Pregnancy						During Labor	10 Days Post-partum	42 Days Post-partum
	4	5	6	7	8	9			
R.B.C.	4.47	4.20	3.93	3.94	4.02	4.04	4.41	4.48	4.75
Hgb.	11.8	11.4	11.0	11.1	11.2	11.2	11.9	12.6	13.2
Hct.	39.5	38.9	37.0	36.8	37.3	37.1	39.3	42.1	42.7
M.C.Hb.	26.2	27.1	28.2	28.4	28.0	28.0	27.2	28.0	27.4
C. I.	.90	.93	.97	.98	.96	.96	.93	.96	.94
M.C.V.	88	93	95	94	93	93	89	94	90
V. I.	.98	1.04	1.06	10.5	1.04	10.4	1.00	1.05	1.01
M.C.Hb.Conc.	29.8	29.4	29.7	30.2	30.2	30.2	30.3	30.0	30.9
S. I.	.91	.86	.91	.92	.92	.92	.92	.92	.94
Minimum Normal Erythrocyte and Hemoglobin Values									
R.B.C.	3.8	3.7	3.6	3.5	3.6	3.8	4.0	4.0	4.2
Hgb.	10.7	10.5	10.2	10.1	10.2	10.5	10.8	10.8	12.0

morphologic criteria. The basis of classification of the common anemias of pregnancy which we employ is as follows:

Iron deficiency anemia: Hemoglobin below 10.0 grams per 100 c.c.
Mean corpuscular hemoglobin below 26 micro-micrograms.
(Color index below 0.9.)

Diet deficiency anemia: Red blood cell count below 3.5 million per cu. mm.
Mean corpuscular volume above 97 cubic microns.
(Volume index above 1.1.)

Anemia of pregnancy associated with inadequate food intake is a true macrocytic anemia and in its more severe manifestations is probably identical with the so-called "pernicious anemia" of pregnancy.[8] Although it has been reported that deficiency of the vitamin B complex may lead to such anemia[9, 10] our results indicate that a closer correlation exists between the incidence of macrocytic anemia and inadequate intake of animal protein than between such anemia and deficiency of either thiamin, riboflavin or the pellagra preventing factor (table 2).

TABLE II

The Relationship of Macrocytic Anemia to the Intake of Animal Protein and the Vitamin B Complex during Pregnancy

Diet	Incidence of Macrocytic Anemia Per Cent
Daily intake of animal protein above 50 grams	00.0
Daily intake of animal protein between 30 and 50 grams	27.3
Daily intake of animal protein below 30 grams	40.0
Daily intake of Vitamin B_1 (Thiamin)—adequate	7.9
Daily intake of Vitamin B_1 (Thiamin)—inadequate	28.9
Daily intake of Vitamin B_2 Complex—adequate	9.4
Daily intake of Vitamin B_2 Complex—inadequate	29.3

In table 3 is given an analysis with respect to incidence and type of anemia of the subjects included in the present study.

TABLE III

Incidence and Type of Anemia of Pregnancy among the Subjects Included in the Present Study

	Number	Per Cent
Cases included in study	158	100.0
Cases with iron deficiency anemia	42	26.6
Cases with diet deficiency anemia	24	15.2
Cases with combined deficiency anemia	19	12.0
Total cases with anemia	85	53.8

Before attempting the evaluation of any form of treatment of anemia during pregnancy an appreciation should be gained of the normal trend of blood values throughout gestation. As stated previously, these changes have been shown to depend, in part, upon varying dilution of the plasma, but that such hydremia is not the only factor responsible for the "physiologic" anemia of pregnancy is indicated by the universal tendency in apparently normal subjects of the mean corpuscular hemoglobin (color index) to decrease appreciably, especially during the early months of gestation, and of the mean corpuscular volume (volume index) to undergo a slight increase. Even in the presence of anemia, untreated, there is usually an

increase in the red blood cells and hemoglobin during the latter months of pregnancy. However, such changes are probably chiefly the mechanical effect of varying concentration, and if observations are made six weeks after delivery it will usually be found that the blood values, especially the hemoglobin, are definitely below the normal range. The trends of erythrocyte and hemoglobin determinations from the beginning of the fourth month of pregnancy to that of the seventh week post partum are shown on chart 1.

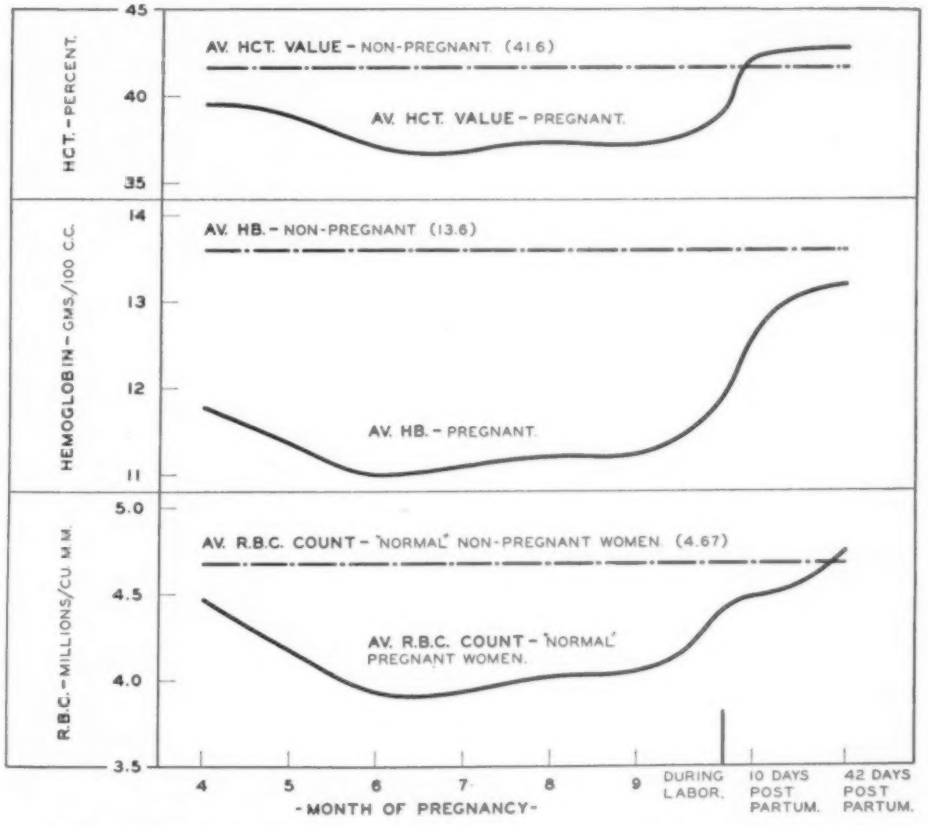

CHART 1. The "physiologic" anemia of pregnancy. Average values based on observations of 30 pregnant women who received no anti-anemia therapy and whose erythrocyte, hemoglobin, and packed cell volume determinations made six weeks after delivery were within normal limits for non-pregnant women. The average normal values for non-pregnant women given here are based on observations at the Simpson Memorial Institute of 100 healthy subjects within the age group of the patients studied.

To determine the effects of iron therapy * the following procedure was employed: 42 subjects with hypochromic anemia and normal or small red blood cells were divided into two groups; to the members of one, comprising 19, ferrous sulphate 0.32 gram three times daily was given, for those of the other, 23 cases, no iron was prescribed. The definite value of medicinal

* The iron preparation employed in this study was supplied by the Eli Lilly Company.

iron for this form of anemia is illustrated in chart 2. Since the period of gestation at which iron therapy was instituted varied between the fifth and eighth months, the contrast between the two groups is best shown by the observations made six weeks after delivery, when the membe s of the treated group were within the range for normal non-pregnant women, with respect to average erythrocyte and hemoglobin determinations, whereas those of the untreated group possessed hemoglobin values averaging 2.6 grams lower than those of the treated subjects. The positive and controlled therapeutic results obtained on these patients appear to us to disprove the contention

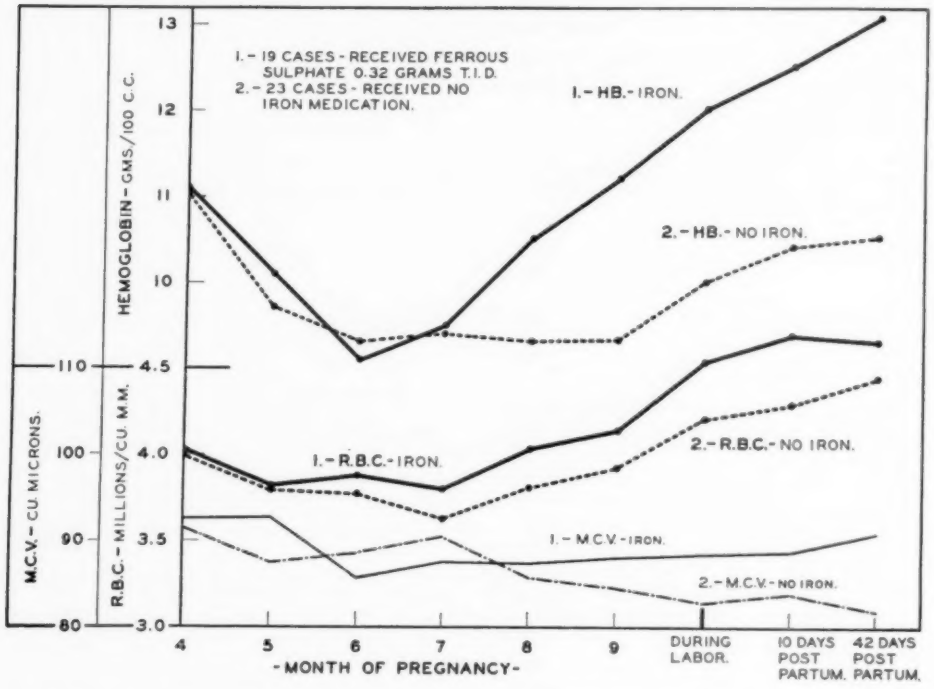

CHART 2. Comparison of the effects of medicinal iron and no therapy on the average erythrocyte, hemoglobin and mean corpuscular volume values of pregnant women with anemia attributed to iron deficiency.

that during pregnancy decline of the hemoglobin to levels appreciably below 10.0 grams per 100 c.c. can be considered physiological.[11] Further evaluation of iron medication in pregnancy was attempted by the selection of 50 women considered, by our standards, to have blood values within the normal range for pregnancy. As in the previous experiment these subjects were divided into two groups of 27 and 23 cases each, and received, respectively, ferrous sulphate and no iron (chart 3). At six weeks post partum the iron treated group possessed an average hemoglobin value 0.3 gram higher than the untreated subjects, but the wider divergence of average hemoglobin determinations at the tenth day post partum suggests that many patients

considered as " normal " with respect to hemoglobin, may nevertheless benefit from iron medication. These observations lead us to agree with the contention of Corrigan and Strauss that routine iron administration throughout pregnancy is justifiable.[12]

The effects of diet improvement on the blood values of 25 patients with macrocytic anemia were determined by dividing the subjects into four groups: (1) six subjects received diet therapy and no iron; (2) seven subjects received no diet instructions and no iron; (3) seven subjects received diet therapy and iron; (4) five subjects received no diet therapy but were given iron.

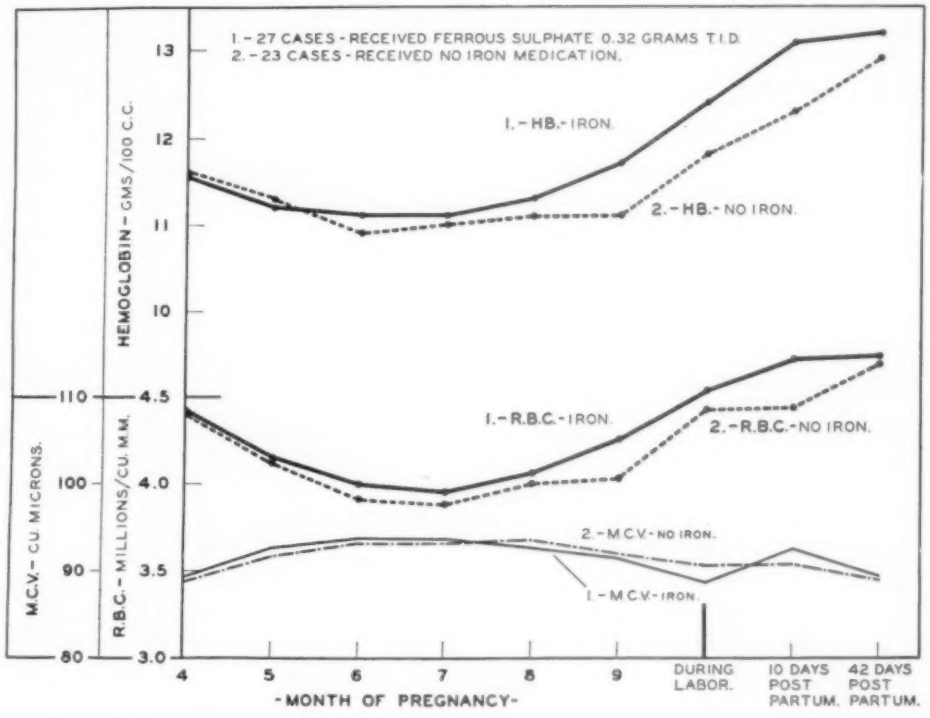

CHART 3. Comparison of the effects of medicinal iron and no therapy on the average erythrocyte, hemoglobin and mean corpuscular volume values of pregnant women without demonstrable anemia.

The hematologic observations on these cases are presented in charts 4 and 5. It should be pointed out that, because of the multiplicity of factors involved and the variable adherence to diet instructions, evaluation of the results of diet therapy in a group of cases is more difficult and somewhat less satisfactory than a similar analysis of the effects of a single form of medication such as iron. Nevertheless, it is clear that improvement in the diet, particularly with respect to the intake of animal protein, was followed by significant increase in blood values, in comparison with the control

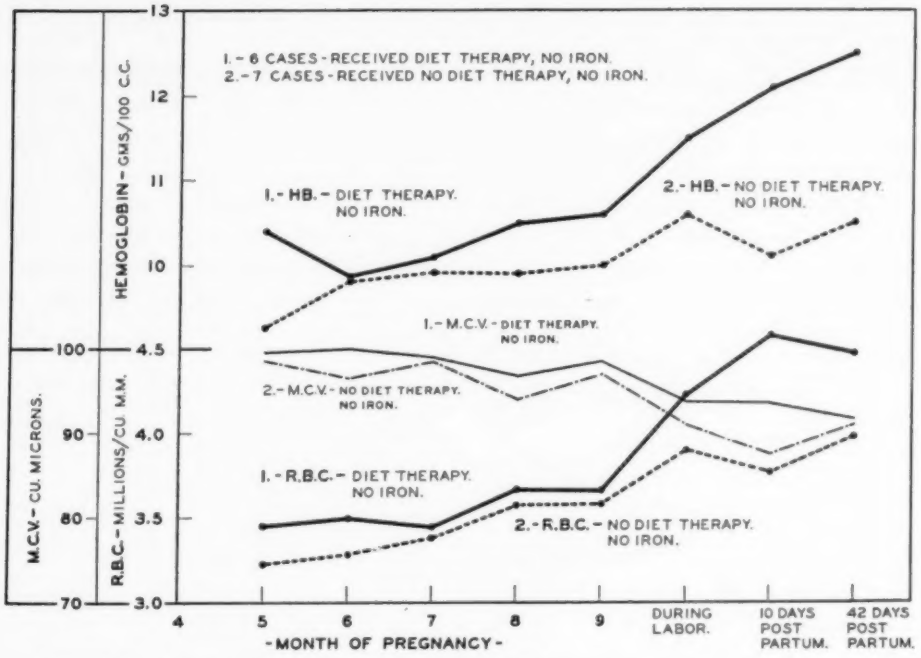

CHART 4. Comparison of the effects of diet improvement, particularly with respect to increased intake of animal protein, and no therapy, on the average erythrocyte, hemoglobin, and mean corpuscular volume values of pregnant women with anemia attributed to dietary deficiency.

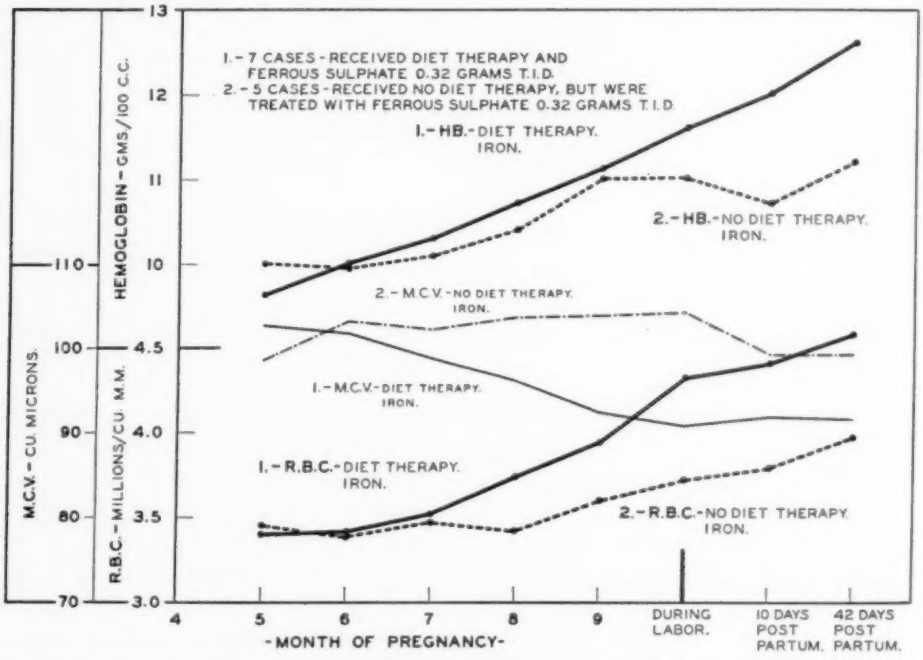
1.-7 CASES-RECEIVED DIET THERAPY AND FERROUS SULPHATE 0.32 GRAMS T.I.D.
2.-5 CASES-RECEIVED NO DIET THERAPY, BUT WERE TREATED WITH FERROUS SULPHATE 0.32 GRAMS T.I.D.
1.-HB.-DIET THERAPY. IRON.
2.-HB.-NO DIET THERAPY. IRON.
2.-M.C.V.-NO DIET THERAPY. IRON.
1.-M.C.V.-DIET THERAPY. IRON.
1.-R.B.C.-DIET THERAPY. IRON.
2.-R.B.C.-NO DIET THERAPY. IRON.
M.C.V.-CU. MICRONS.
HEMOGLOBIN-GMS./100 C.C.
R.B.C.-MILLIONS/CU. M.M.
-MONTH OF PREGNANCY-
DURING LABOR.
10 DAYS POST PARTUM.
42 DAYS POST PARTUM.

CHART 5. A study similar to that shown on Chart 4 except that all subjects were given medicinal iron.

groups, whether or not iron was also prescribed. However, the more uniform rate of increase of both red blood cells and hemoglobin when iron was given in conjunction with improved diet suggests that the metal may be of supplementary value in the treatment of anemia of pregnancy attributed to dietary deficiency.

Conclusions

The incidence of true anemia of pregnancy is high, amounting to 54 per cent of 158 clinic cases studied. Such anemia most often results from deficiency or impaired utilization of iron. A second important cause is inadequacy of the diet, particularly with respect to its content of animal protein.

Hemoglobin values, in pregnancy, below 10.0 grams per 100 c.c. are probably never "physiological," and in the presence of lowered mean corpuscular hemoglobin or color index indicate a lack of available iron. Red blood cell counts below 3,500,000 per cubic millimeter associated with macrocytosis suggest protein deficiency. Not infrequently a combined type of anemia is present, presumably dependent upon a need for both iron and protein.

Inorganic ferrous preparations are the most effective and least irritating forms of medicinal iron for use in the treatment of the hypochromic anemia of pregnancy. Since the detection of slight degrees of iron deficiency during gestation is difficult, and the evidence presented indicates that the majority of pregnant women derive benefit from iron medication, it is justifiable to administer iron routinely throughout pregnancy.

A diet supplying approximately 50 grams of animal protein daily, in addition to adequate amounts of other "protective" foods, is effective in correcting anemia of moderate degree attributed to dietary deficiency. In the treatment of more severe macrocytic anemia of pregnancy the daily intake of animal protein should be adjusted to a level of 1.5 grams per kilo.

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TREATMENT OF THE STOKES–ADAMS SYNDROME BY HYPERTONIC GLUCOSE SOLUTION GIVEN INTRAVENOUSLY *

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Although the symptom complex grouped under the heading of the Stokes-Adams syndrome may be caused by many conditions which produce temporary cerebral anemia, we will confine our discussion only to the two main conditions, namely stoppage of the heart and ventricular fibrillation. Furthermore, we shall eliminate from our discussion those cases of sino-auricular standstill or auriculo-ventricular block caused by direct or reflex vagal inhibition which can be abolished or successfully treated by atropine. This leaves us a group of cases where for some unknown reason there is a sudden interruption in the passage of the electrical impulse from the auricles to the ventricles, resulting in complete ventricular stoppage, or the sudden onset of ventricular fibrillation. The condition usually occurs in individuals where partial auriculo-ventricular block already exists.

The treatment of the condition has been unsatisfactory in the past, and the effects of the therapeutic measures employed have been contradictory. Barium chloride has long been discarded as useless. Adrenalin and ephedrine have been found to have beneficial effects in cases where the ventricles stop, but some investigators as Dock [1] and Schwartz and Jezer [2] found that these drugs may induce attacks of ventricular fibrillation. On the other hand, some authors as Phear and Parkinson,[3] Levine and Matton [4] and Cahall [5] claim good results from adrenalin even in ventricular fibrillation. The use of quinidine in ventricular fibrillation likewise has its supporters and antagonists. Levine [6] found experimentally that quinidine prevents ventricular fibrillation. Dock [1] and Escamille [7] found it of value in clinical ventricular fibrillation. Kerr and Bender,[8] Schwartz and Jezer,[9] Davis and Sprague [10] and Cahall [5] on the other hand found that the drug induces ventricular fibrillation. In one of my cases of Stokes-Adams syndrome due to transient ventricular fibrillation, both quinidine sulphate and adrenalin brought about attacks with greater frequency, and each attack was more prolonged and more severe. In another case adrenalin seemed to have good effects.

One of the reasons for our therapeutic inefficiency in this condition is that we do not know what changes take place in the heart which bring about the sudden interruption of conduction or the sudden onset of ventricular fibrillation. That vagal hyper-activity plays no part is evidenced by the fact that no amount of atropine given during an attack relieves the condition. It appears to be due to local circulatory stasis and edema of the auriculo-ventricular node, the bundle and bundle branches, resulting in sudden inter-

* Received for publication September 14, 1937.

ference with nutrition and oxygenation of this delicate apparatus. This could conceivably produce disturbances in conduction and in some cases the initiation of multifoci of irritability culminating in a circus movement in the ventricles and ventricular fibrillation. The circulatory changes may be analogous to those seen in partial occlusive vascular disease of the extremities.

If this conception is correct, a concentrated solution of any crystaloid injected intravenously which would tend to act as a tissue dehydrant should give relief. Of these a concentrated glucose solution appeared to me to be the best for the purpose. Since its value was first demonstrated in the relief of intraocular tension in glaucoma by Hertel [11] in 1915, and in the relief of increased cerebro-spinal pressure by Weed and McKibben [12] in 1919, many reports appeared in the literature substantiating its value as a tissue dehydrant. I felt that in addition to its dehydrating effect it also has nutritive value. I have accordingly tried the use of 50 c.c. of a 50 per cent glucose solution, administered intravenously in four cases of Stokes-Adams syndrome. All four exhibited auriculo-ventricular dissociation, two with complete stoppage of the ventricles and two with ventricular fibrillation. The results appear to be very promising.

Although concentrated glucose solution given intravenously is used in some cardiac conditions, I did not find any reference of its use in the Stokes-Adams syndrome. For this reason and with the hope that it may prove to be of value in the treatment of this desperate condition, I offer this communication.

The following are short summaries of the four cases. Electrocardiographic studies of Case 1 and Case 3 were reported in full detail elsewhere.[13, 14]

Case Reports

Case 1. L. F., male, 58 years old, was first seen by me on March 7, 1936. He presented at that time definite clinical and electrocardiographic evidence of arteriosclerotic heart disease with the anginal syndrome. There was partial auriculo-ventricular block and marked delay in the intraventricular conduction time. Under appropriate therapy he showed improvement in his subjective symptoms until November 11, 1936, when he was found in the bathroom in an unconscious state and in convulsions. Since then there was a gradual and progressive increase in frequency, severity and duration of attacks of unconsciousness and convulsions. Some days he had as many as 20 such attacks in 24 hours. An electrocardiogram taken just before and during one of these attacks showed complete auriculo-ventricular dissociation, multifoci ectopic ventricular impulses followed by ventricular fibrillation. During the fibrillatory period, no heart sounds could be heard, and unconsciousness and convulsions would ensue. Quinidine sulphate aggravated the condition as did adrenalin and ephedrine. On December 22, he received 50 c.c. of 50 per cent glucose solution intravenously. During that day the attacks greatly diminished in intensity and frequency. There were merely transient dizziness and short periods of stupor but only very occasionally were there complete unconsciousness and convulsions. He was getting along fairly well for about 10 days thereafter on an occasional repetition of the intravenous glucose. On the eleventh day, however, he suddenly died during an attack of convulsions.

Case 2. J. A., male, 57 years old, who claimed to have been in good health previously, suddenly developed precordial pain and recurring attacks of transient loss of consciousness, some of which were rather prolonged and accompanied by convulsions. He was admitted to my service at the Harbor Hospital. The heart between the attacks showed a regular sinus rhythm with a rate of about 96 to 105 beats per minute, and there was no enlargement. The first sound was muffled and hardly audible, and there was a presystolic gallop rhythm. The second heart sound was likewise very weak. The electrocardiogram (figure 1) during an attack showed a sudden change

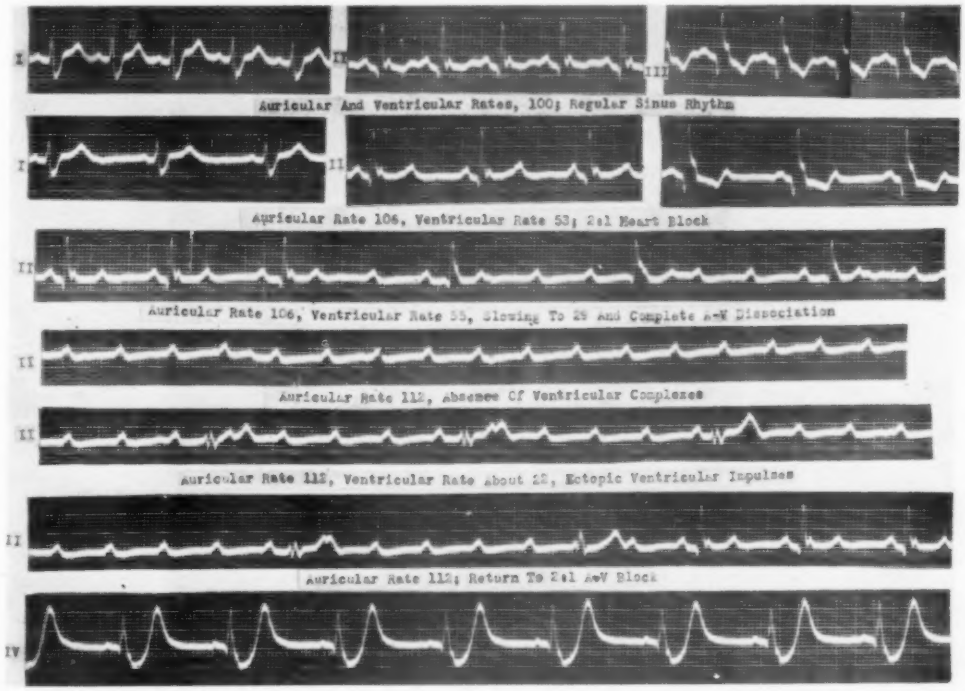
I
II
III
Auricular And Ventricular Rates, 100; Regular Sinus Rhythm
I
II
Auricular Rate 106, Ventricular Rate 53; 2:1 Heart Block
II
Auricular Rate 106, Ventricular Rate 35, Slowing To 2:1 And Complete A-V Dissociation
II
Auricular Rate 112, Absence Of Ventricular Complexes
II
Auricular Rate 112, Ventricular Rate About 28, Ectopic Ventricular Impulses
II
Auricular Rate 112; Return To 2:1 A-V Block
IV

FIG. 1. *Electrocardiograms in Case 2.* Regular sinus rhythm with normal auriculoventricular conduction time followed by partial, then by complete auriculo-ventricular dissociation, and ventricular standstill. The intraventricular conduction time is about 0.15 second. The reappearance of the ventricular impulses are at first of the ectopic type and are later followed by the regular supraventricular type. The fourth lead (old standard method) shows grossly abnormal complexes associated with acute coronary occlusion.

from regular sinus rhythm and normal auriculoventricular conduction to partial 2:1 block and then a gradual increase in block with slowing of the ventricles until complete auriculoventricular dissociation and stoppage of the ventricles ensued. At this period loss of consciousness would occur followed by convulsions if the ventricles were at a standstill for half a minute or longer. These episodes of unconsciousness and convulsions recurred at very frequent intervals, at times as many as four attacks in one hour.

Because of the suddenness of onset with precordial pain and the disturbed auriculo-ventricular condition, the diagnosis was made of acute coronary occlusion, affecting most likely the right coronary artery and the ramus septi fibrosi.

An intravenous injection of 50 c.c. of 50 per cent glucose was given with almost miraculous results. There was no recurrence of auriculo-ventricular block. He re-

mained in the hospital nine weeks, and showed the characteristic clinical manifestations of acute coronary occlusion, that is, apical pericardial friction rub on the second day, temperature reaction, high leukocyte count and rapid sedimentation rate. The electrocardiogram likewise showed characteristic changes. At no time during those nine weeks did he have any recurrence of the Stokes-Adams syndrome. The rhythm was of normal sinus origin, rate about 80 to 96, and the auriculo-ventricular conduction time remained normal. The last I heard from him, about three months after his discharge from the hospital, was that he felt well.

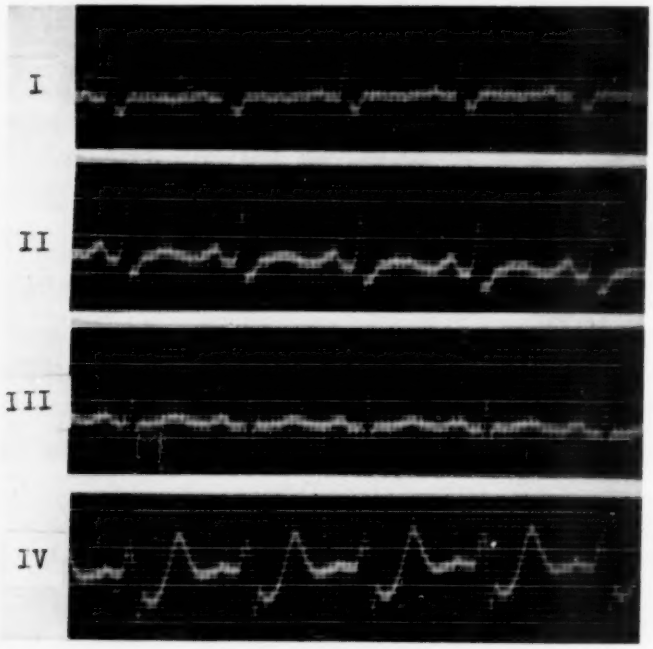

FIG. 2. Same case, one week later. Regular sinus rhythm with normal auriculo-ventricular conduction time. There are changes in the ventricular complexes in all leads, as compared with the previous tracings.

Case 3. E. S., female, 66 years old, seen by me on May 30, 1937, had mild diabetes for 10 years and hypertension for at least seven months. During the latter period she had recurring episodes of the anginal syndrome associated with ringing in the ears, and in four weeks she had four attacks of unconsciousness and convulsions. The first one recurred almost continuously for about five hours and was finally relieved by 1 c.c. of adrenalin given subcutaneously. The attacks recurred three days after and became very frequent. Any slight manipulation such as taking the blood pressure would induce an attack. There was complete auriculo-ventricular dissociation with an idioventricular rhythm of the supraventricular type and intraventricular block. Multifoci ectopic ventricular impulses occurred followed by periods of ventricular fibrillation. During the fibrillatory period the heart sounds were not audible, the pulse could not be felt and unconsciousness and convulsions ensued. The attacks became milder and recurred less frequently the following three days after repeated intravenous injections of 50 c.c. of 50 per cent glucose solution were given. For three weeks thereafter there was no recurrence of the Stokes-Adams syndrome. She finally died during a severe attack.

Case 4. S. J., male, 67 years old, with a history of hypertension for many years, suddenly became unconscious and went into convulsive seizures while at rest in bed. These attacks recurred about eight times in the following 24 hours and became more severe and prolonged each time.

He presented generalized arteriosclerosis. The heart was moderately enlarged to the left and the aortic arch was markedly widened. A harsh systolic murmur was heard at the third left costosternal junction transmitted to the base, neck and downwards as far as the apex. The heart rate between attacks was 76, rhythm regular. There was a prolongation of P–R conduction time to 0.26 sec. At the onset of the attack there was a gradual prolongation of the P–R conduction time to as high as 0.48 second, with a dropping out of ventricular beats and soon there was complete stoppage of the ventricles while the auricles continued beating at the same rate as previously. During this period, unconsciousness and convulsions would occur. There was no evidence of failure of either the right or left ventricle.

Glucose solution given intravenously resulted in complete stoppage of attacks. Two months have now elapsed with no recurrence of complete block and the Stokes-Adams syndrome. The rhythm is of regular sinus origin but the P–R conduction time is still 0.26 second. Aside from the anginal syndrome in a moderate degree, he is fairly comfortable.

Comment

Because the Stokes-Adams syndrome has a tendency to subside spontaneously for variable periods, our conclusions as to the value of any medication in this condition must be guarded. There is, however, no doubt that the four cases recorded in this paper on whom hypertonic glucose solution was used have definitely benefited by it.

That the benefit is not permanent, and that sooner or later termination of life by the disease will ensue is to be expected from the nature of the underlying pathology. The four patients presented here all had advanced arteriosclerotic heart disease which is a progressive condition. In all these cases, constant physiologic changes undoubtedly occur in the vascular supply to the heart muscle in the form of stasis, venous engorgement, transient spasm and so on. For this reason any medication which might be of benefit can not be well timed in its application. We can employ it only when gross subjective or objective manifestations of disturbances are evident. We must, therefore, not expect the use of hypertonic glucose solution to be always successful in preventing attacks. If it affords relief and prolongs life, however, it is worth further trial in as serious and often as hopeless a condition as the Stokes-Adams syndrome.

This method of treatment is definitely more efficacious in Stokes-Adams syndrome caused by ventricular stoppage than that caused by ventricular fibrillation. In the former condition it appears to have a permanently beneficial effect, judging from the two cases recorded here.

I have not had the opportunity to try it in younger individuals where the heart disturbance may be caused by infections. In such instances it will probably prove to be of greater value.

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SUDDEN AND UNEXPECTED DEATH FROM ACUTE INTERSTITIAL MYOCARDITIS; A REPORT OF THREE CASES *

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The causes of sudden and unexpected death occurring in individuals in apparent good health frequently require microscopic study for their elucidation. A miniature or inconspicuous lesion may be the main factor in such a type of death with the result that sometimes painstaking search is required to find it. Such cases are not only of scientific interest but they may have far reaching forensic implications.

Focal interstitial myocarditis as the cause of death is a relatively uncommon condition and, as the cause of sudden and unexpected death, it appears from the study of the reported cases to be quite rare. Simon and Walpaw [1] recorded 48 cases in 1935 and added one of their own. Since then Scott and Simon,[2] Hirai [3] and Kjaergaard [4] have reported single cases, making a total of 52 in the literature to 1938 which had been proved by necropsy studies. In this group there were but eight instances where death was more or less sudden in character.

Recently we have studied three cases of sudden and unexpected death in which the mechanism was acute cardiac failure with pulmonary edema and the cause of this cardiac death was discovered only after careful microscopic study of the myocardium.

Case Reports

Case 1. Mr. C. E. B. H., 32 years old, an electric driller, was working on a scaffold about 10 feet from the ground when he suddenly fell down on the scaffolding unconscious. When first examined by a physician his heart was not beating and adrenalin injected into the left ventricle failed to produce any palpable or audible cardiac impulse. He was taken to a hospital where he was pronounced dead. Interrogation of his family and associates was negative for any history of previous illnesses. Because of the fact that he was working with an electric drill, the possibility of electrocution was considered and on careful investigation of the drill a short circuit was found. It was the impression of those who saw the entire picture of the sudden fall that he died instantaneously or at least very shortly after the fall.

Necropsy

Examination was performed 16 hours after death. The arterial embalming had been done within one hour after death. At the necropsy examination the subject was found to be a very large man weighing about 210 pounds and measuring about 6 feet 1 inch in length. The only findings of interest were confined to the chest. The heart weighed 410 grams and showed a moderate degree of dilatation of all the chambers. There was a persistent thymus present and the aorta was a typical *aorta*

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angusta. No blood was present in the pericardial sac even though the needle puncture had penetrated into the right ventricle thus suggesting that the heart had stopped beating when the adrenalin was administered. There were about 50 c.c. of free fluid in each pleural cavity and the lungs were the seat of marked edema and clear frothy fluid poured forth from the cut surface. There was an intense acute hyperemia of all the viscera. One small hemorrhage about the size of a quarter of a dollar was found in the pulmonary parenchyma. No other abnormalities were encountered after a thorough search except for two small red spots above each external malleolus and above each radial prominence on both wrists. These measured from three to four millimeters in diameter and were moderately desiccated. The question of possible current marks was eliminated by subsequent histological examination and inasmuch as a depression was present on the skin in these regions it was considered that they

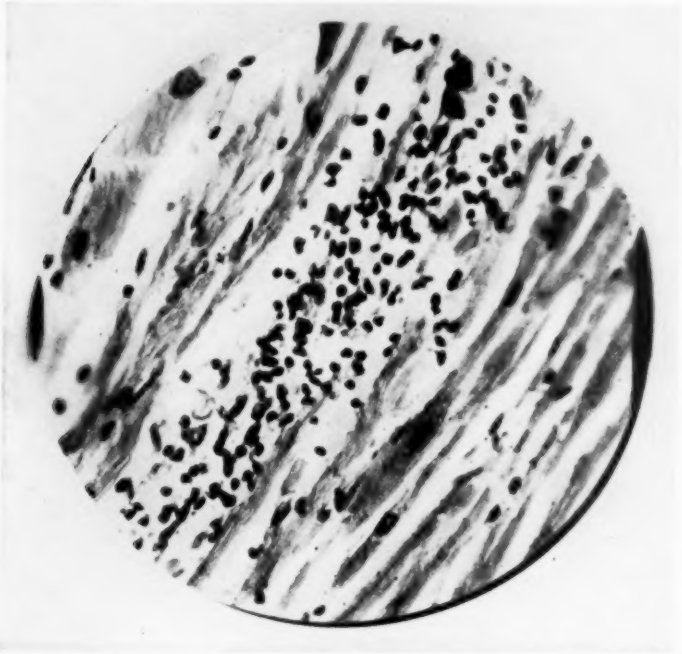

FIG. 1. *Case 1.* High power photomicrograph showing focus of interstitial inflammation in the myocardium.

represented areas where the hands and feet had been tied with cord after death. The brain and spinal cord were negative.

Histologic Pathology. The heart muscle fibers were hypertrophied and about many of the small blood vessels there was a mild degree of interstitial edema. A rather striking segmentation of many of the muscle fibers was also found. Some of the small blood vessels showed swelling of the intimal endothelium. A rare focus of acute and chronic inflammatory cells was found after prolonged search. These foci showed breaking up and disintegration of the muscle fibers. The inflammatory cells in these foci were largely mononuclear cells although occasional polymorphonuclear leukocytes and plasma cells were seen. There was loss of cross striation of the muscle fibers in these foci and in the body of the fiber, granular changes and fragmentation of the cytoplasm were seen. The auricular muscle showed scattered round cells in the stroma between the fibers.

The lung showed dilatation of the inter-alveolar capillaries from acute congestion and the larger vascular channels were likewise engorged. In some of the alveoli a homogeneous pink albuminous precipitate was found.

The other viscera showed nothing histologically noteworthy.

Case 2. Mr. P. B., 43 years old, a laborer, on the day of his death had been painting the inside of a tank with gilsonite asphaltum paint. The paint was thinned with petroleum naphtha. A heavy stream of air was running through the tank at all times and he was in the tank on only two occasions at intervals of ten and eight minutes respectively. Four other men were working in the tank painting and none of them suffered any untoward symptoms. He emerged from the tank with his partner and rested some 30 minutes, worked around the plant in the open air for about

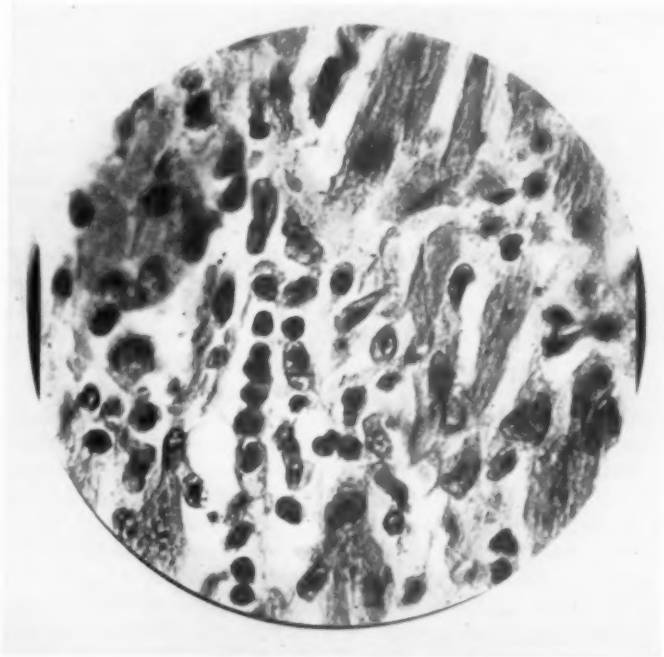

FIG. 2. *Case 2.* Oil immersion photomicrograph showing myocardial inflammation. Note character of cells and breaking up of muscle fibers.

an hour and then went home with a friend. At no time during the period when he was working in the tank or thereafter while working about the plant did he complain or show any visible evidence to his associates of anything abnormal in his behavior. When he arrived at home, his wife stated that he fell to his knees when he entered the front door, began to froth at the mouth and suffered paroxysms of coughing. A doctor was summoned who gave him morphine and atropine which produced temporary relief. An examination of his chest at this time revealed signs of advanced pulmonary edema. Two hours after this paroxysm another of similar character occurred and morphine and atropine were again administered, this time without much relief. Shortly thereafter the patient began to show signs of more striking pulmonary edema and died. He arrived home about five o'clock in the evening and died about eleven o'clock that night. The only possibly significant history obtainable was to the effect that eleven years previously he had been in a hos-

pital for a few days because of an attack of the influenza. At this time the hospital record showed that he had an irregular pulse. No other history was obtainable of any intercurrent sickness up to the afternoon of his death.

Necropsy

Examination was conducted 12 hours and 45 minutes after death. The body had been arterially embalmed within one and one-half hours after death. At the necropsy the gross findings were all essentially negative with the exception of the heart and lungs. The heart was found to be of about normal size for a man of this age, general stature and development. It weighed 308 grams and on external inspection was negative except for a moderate dilatation of all the cardiac chambers. There were about 100 c.c. of clear fluid in each pleural cavity and the lungs were strikingly edematous so that fluid ran freely from the cut section. Aside from a subendocardial hemorrhage in the left cardiac ventricle, small petechial hemorrhages in the gastric mucosa and a moderate atherosclerosis of the descending branch of the left coronary, no other findings of interest or importance were observed. The brain and spinal cord were negative.

Histologic Pathology. Fifteen different blocks were sectioned from various areas throughout the myocardium. The largest number were taken through the interventricular septum. In all sections extensive fragmentation and segmentation were present. Some hypertrophy of occasional fibers and some *lipomatosis destruens* were also present but the most striking feature of the reaction was the extensive fragmentation. Sometimes between these groups of fragmented and segmented fibers an edematous fluid was encountered made up of a pink staining albuminous precipitate. In some areas fat tissue had extended deeply into the myocardium. In one area an old hyaline scar was seen. Here the muscle fibers had been replaced by hyalinized, almost anuclear connective tissue. Of most importance were two foci of acute and chronic interstitial myocarditis, consisting in each instance of a small focus of infiltrating leukocytes which under the higher magnification were found to be chiefly lymphocytes although occasional plasma cells were also present. These foci of cells were separating the myocardial fibers and in one area the fibers had lost their nuclei.

Sections through the lungs, taken in different areas, showed a very high grade edema; the alveoli were filled with a homogeneous pink staining precipitate. Occasionally wandering polymorphonuclear leukocytes were found which had escaped into this fluid in the lumen of the alveolus. Occasionally also fibrin strands enmeshing polymorphonuclear leukocytes were seen in the alveoli. There was some infiltration of polymorphonuclear leukocytes beneath the mucosa of the bronchi and trachea. The mucosa itself was intact for the most part and the leukocytes were present both in the blood vessels and in the interstitial tissue. Round cells, plasma cells and interstitial edema were likewise seen in the submucous connective tissue beneath the bronchial epithelium.

The liver showed some fine pigment granules in the parenchymal cells about the central veins and there was some pigment phagocytosis of the cells of the splenic pulp.

The thyroid gland showed a definite overgrowth of the acinar epithelium. The cells were cuboid or columnar and the colloid pale and peripherally vacuolated. The gland grossly was but moderately enlarged. Otherwise, aside from a small congenital hemangioma of the liver and mild atherosclerosis of the descending branch of the left coronary artery, nothing of histological moment was encountered.

Case 3. A 13 year old boy entered the hospital for a foot operation. Complete physical and laboratory examination showed no variation from the normal except for the feet. The heart sounds and rate were normal and of good quality and the rhythm was regular. No murmurs were elicited. The lungs were clear and resonant. No râles were heard. The abdomen was negative. He underwent an operation for

rigid left foot and a flexed cleft foot on the right. Bilateral heel tendon lengthening and lengthening of the left perineals were carried out. He was under cyclopropane anesthesia for 1 hour and 35 minutes and left the table in excellent condition with a pulse rate of 74. Throughout the day he appeared to be having a normal recovery from his operation when suddenly at 11:15 p.m. of the day upon which the operation took place, his pulse became very rapid and when first counted was 150 per minute. He began to develop signs of pulmonary edema. The pulse became even more rapid and weak and signs of pulmonary consolidation, particularly on the right side, became striking. A diagnosis of possible pulmonary embolism was made. At 8 a.m. the following morning the temperature was 103° F. axillary and the respiratory rate was forty. Edema became more advanced and the patient expired at 1:55 p.m., 27 hours after his operation. No history of any previous cardiac disturbance was elicited from the family. The only information that was obtained was to the effect that the boy had never been robust and had always failed to take part in the more strenuous games with his associates.

Necropsy

Examination was conducted 35 minutes after the patient expired. No embalming had been done. A moderate degree of cyanosis was present. No other findings on external examination were of importance. In the chest the heart showed wide dilatation of all its chambers. It weighed 175 grams. The muscle was flabby and the *columnae carneae* were flattened. The heart was opened in situ and the pulmonary artery was investigated for possible embolism but none was found. On the surface of the epicardium a very delicate, semi-granular exudate was visible suggesting a beginning pericarditis. About 50 c.c. of free fluid were found in both pleural cavities and the lungs were the seat of a very marked edema and advanced posterior congestion on both sides. In the dependent areas of both lungs, small hemorrhagic foci of semi-consolidation were seen on cross section which suggested a very early pneumonic infiltration. In the left axillary line region over an area measuring about 10 by 5 cm. healing, hyalinized tubercles and adhesions were present. The hilar lymph nodes were the seat of a fibro-caseous tuberculosis and multiple miliary healed subcapsular tubercles were found in the liver. There was a persistent thymus, a relatively small aorta and operative incisions on both feet. There was no evidence of pulmonary embolism, nor of thrombosis in the veins of the legs.

Histologic Pathology. Numerous sections were taken through the heart. In most instances the myocardial fibers showed some cloudy swellings and some separation of the fibers as well as a moderate degree of fragmentation and segmentation. None of these changes were particularly striking. However, in some areas there was a slight increase of connective tissue of a loose, edematous character about the blood vessels and occasionally the endothelial lining of these vessels was swollen and almost exfoliated. In some areas, particularly in the auricular muscle, there was wide separation of many of the fibers. Occasional small areas were seen where there were small scar foci about the blood vessels. One or two areas were found where there was an infiltration with polymorphonuclear leukocytes into subepicardial fat. Rare focal infiltrations of both round cells and polymorphonuclear leukocytes were found in the myocardium. These focal infiltrates were characteristic of an acute and chronic interstitial myocarditis. The muscle fibers in these focal areas were degenerated and fragmented and had lost their striations.

The lungs showed an early broncho-pneumonia superimposed upon a massive edema. The alveolar exudate was rich in pus cells and very little fibrin was present, although considerable serum and many red cells were found. Most of the pus cells were in an excellent stage of preservation. Healed hyalinized tubercles with a central area of caseation were found beneath the pleura. These tubercles were very numerous in the pleura but none were found in the lung parenchyma.

The liver showed caseous tubercles with a thick fibrous capsule about them. The liver cells showed only a mild degree of cloudy swelling and no passive congestion.

The spleen showed occasional miliary tubercles in the pulp. These tubercles were made up largely of masses of endothelioid cells without caseous centers. The sinusoids were quite prominent.

The other organs presented no noteworthy variation from the normal.

Comment

In the first case death was apparently almost instantaneous but the factor of electrical shock may have been a feature in the sudden cessation of heart action. In the second case, which like the first was of forensic as well as scientific interest, a careful analysis of the ingredients of the paint used showed that the only toxic substance in the paint was naphtha. It was considered that the inhalation of the paint was of no consequence in the heart failure inasmuch as there was no manifestation of naphtha intoxication found at the necropsy. The brief period of exposure to which the patient had been subjected to the fumes of naphtha and particularly the absence of symptoms in other workers confirmed this belief. Moreover, this man had worked in the open air for almost an hour after leaving the tank painting job and did not show any evidence of heart failure until he reached home. The symptoms of acute pulmonary edema were the only findings other than a rapid pulse that presented themselves throughout the short period he was alive after the onset of his cardiac failure. The only history of any possible previous cardiac damage was that obtained from a hospital admission record some 11 years prior to his death when a diagnosis of influenza was made and an occasional extrasystole was discovered on examining the chest. The possible relationship of a moderately toxic thyroid gland should be considered.

In the third case the symptoms of cardiac failure did not become clinically manifest until 12 hours after operation and these symptoms grew progressively more pronounced until the patient died some 15 hours after the onset of cardiac failure. Any possible relation of the prolonged cyclopropane anesthetic to the heart failure would be pure speculation. No evidence in the other viscera, such as the liver, showed any toxic change.

Discussion

Acute interstitial myocarditis has been reported in infants and the aged but the majority of cases have occurred between the ages of 20 and 50. There have been no characteristic clinical findings in the cases which were studied over any period of time. As a rule the history has been that of rather rapid and progressive myocardial failure. The etiology is unknown, although infections, such as syphilis, rheumatic fever, influenza, gonorrhea, measles and remote infections and burns have been blamed. In many instances there was neither clinical evidence nor a past history of any infec-

tious process and careful bacteriological and histological studies of the myocardial lesions have not been successful in revealing any consistent etiological factor.

Interstitial myocarditis should receive serious consideration in any case of sudden and unexpected death where at necropsy the naked eye examination reveals no anatomic lesion which could be held responsible for the sudden exit. Moreover, it should be emphasized that it may require a very careful and sometimes painstaking microscopic study of the myocardium before this lesion can be found. In all three of the cases which we have just recorded a complete necropsy examination was conducted which in two instances included a careful study of the brain and spinal cord and the only possible cause of death was found only after careful search of many microscopic sections of the myocardium. A moderately dilated heart and pulmonary edema were the only gross findings which led us to conduct such searching histologic investigation.

Very little information has been obtained from electrocardiographic studies on those patients where these were undertaken. De la Chapelle and Graef [5] observed "a prolonged PR interval, complete intraventricular block and low voltage in all leads with a normal sinus rhythm, while Scott and Saphir [6] observed only a left ventricular preponderance."

Among the cases of sudden death from acute interstitial myocarditis, the following have been reported: In 1898 Freund [7] observed a patient who had been suffering for many months with polyarthritis. This patient suddenly went into coma and died. In 1901 Zuppinger [8] was treating a patient for infection in the groin. This patient was suddenly seized with cramps and died.

Saltykow [9] in 1905 reported an instance where the subject, while undergoing treatment for burns, died suddenly. There were no visceral changes aside from those observed in the heart.

In 1921 Fiebach [10] recorded an instance where a patient entered the hospital with acute cardiac failure and died the following day. In the same year von Gierke [11] reported a case of a 25 year old servant girl apparently in normal health who died suddenly while beating a carpet.

Lemke [12] in 1924 first saw his patient in acute cardiac failure and the same was true of Schminche's case.[13]

In 1929 Legrand and Nayrac [14] reported a case of a patient 69 years old who died of rupture of the left ventricle four days after seeming to recover from a convulsion.

Thus, in a series of 52 reported instances of acute isolated interstitial myocarditis there were but eight cases that died unexpectedly and suddenly. Although quite rare when considered from the standpoint of the number of reported cases, nevertheless interstitial myocarditis does constitute a definite, important and perhaps not infrequently unrecognized cause of sudden death.

Conclusion

Three cases of acute interstitial myocarditis causing sudden and unexpected death are reported. In all instances a laborious microscopic examination of the myocardium was necessary before the lesion was found. The necessity for painstaking histologic investigation of the myocardium in sudden death is obvious.

Acute interstitial myocarditis may be the sole cause of sudden and unexpected death.

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THE INCIDENCE OF PNEUMOCOCCUS TYPES AND THE RELIABILITY OF THE NEUFELD TYPING METHOD *

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FOLLOWING the separation of Group IV pneumococci into 29 serologically distinct types by Cooper and her co-workers,[1] a fresh study of the type distribution of pneumococci in different localities has become necessary. Reports of such investigations have appeared from Boston,[2] New York,[3] Cincinnati,[4] and San Francisco.[5] It is the purpose of the present paper to show the incidence of the various types of pneumococci in patients with pneumonia and also in other persons in the District of Columbia.

MATERIALS AND METHODS

All specimens of sputum examined in the Health Department Laboratory and in the Central Laboratory of the George Washington University Hospital, and found to contain pneumococci, are included in this study. Sputums were obtained from patients in the adult wards of Gallinger Municipal Hospital and other hospitals in the city, and from private patients, both at their homes and in hospitals. Accordingly, a fair cross-section of the adult population of the City of Washington is represented.

Typing by the Neufeld technic was performed at the beginning of the study by using only Types I, II, V, VII and VIII rabbit serum, but later tests were performed by this method for all types. In nearly every case (and in every case in which a type was not found by the Neufeld method), the Neufeld typing was followed by the injection of sputum into a white mouse. The peritoneal exudate and a culture from the heart's blood of the mouse were typed by macroscopic agglutination using horse serums for all types (kindly furnished by the late Miss Georgia Cooper). If the types found in a previous sputum or other specimen from the same patient corresponded with the type found by the Neufeld method, typing by the mouse method was usually not carried out.

For the Neufeld test we have used both the hanging-drop method originally described by Sabin,[6] and also the method of placing the sputum-serum mixture flat on a slide under a cover-slip, as proposed by Beckler and MacLeod.[7] Both methods have worked well. The latter method is the quickest and simplest. The hanging-drop method, on the other hand, has the advantage of not drying up when it is kept for several hours. Occasionally

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we have obtained a "quellung" after this interval which did not appear earlier.

Results

In table 1 are shown the results of sputum typing in 445 persons, composed of 302 cases of lobar pneumonia. Fifty cases of pneumonia of atypi-

Table I

Pneumococcus Types in Relation to Disease

Type	From Pneumonia						From Other Sources	
	Lobar Pneumonia		Atypical or Broncho-pneumonia		Total Pneumonias		Lung Abscess and Bron-chitis	Carriers
	No.	%	No.	%	No.	%	No.	No.
I	86	29	2	4	88	25	0	1
II	14	5	0	0	14	4	0	0
III	23	8	8	16	31	9	2	4
IV	11	4	3	6	14	4	0	2
V	21	7	0	0	21	6	0	0
VI	9	3	3	6	12	3	1	4
VII	22	7	3	6	25	7	0	2
VIII	25	8	4	8	29	8	1	1
IX	4		5		9		0	4
X	6		2		8		0	11
XI	6		0		6		2	2
XII	9		1		10		1	2
XIII	4		2		6		0	2
XIV	6		1		7		0	3
XV	1		0		1		1	4
XVI	5		2		7		1	4
XVII	4		1		5		1	4
XVIII	5		1		6		1	2
XIX	10		0		10		0	6
XX	0		1		1		2	2
XXI	5		0		5		0	1
XXII	6		1		7		0	3
XXIII	2		1		3		0	2
XXIV	0		4		4		1	5
XXV	6		1		7		0	1
XXVII	3		1		4		0	1
XXVIII	2		2		4		0	1
XXIX	3		1		4		0	2
XXXI	3		0		3		0	2
XXXII	1		0		1		1	1
Total	302		50		352		15	79

cal distribution (often called bronchopneumonia), 15 cases of other lung infections in which pneumococci were presumably etiologically connected, and 79 cases in which there was no pneumococcal respiratory disease. The last group included patients who had tuberculosis, simple coryza, or a non-respiratory disease, or who were normal individuals.

Type I pneumococci were found in 29 per cent of the cases of lobar and 4 per cent of the cases of atypical pneumonia. Type II pneumococci caused 5 per cent of all lobar pneumonias and no bronchopneumonias. Types V, VII and VIII pneumococci accounted for 7, 7 and 8 per cent, respectively, of the lobar pneumonias, and 0, 6 and 8 per cent of the atypical pneumonias. In contrast to the foregoing types, Type III pneumococci were responsible for 8 per cent of the lobar pneumonias and 16 per cent of the atypical pneumonias. Pneumococci Types IV, VI and Types IX through XXXII were each responsible for a smaller percentage of the total cases of pneumonia, and were found to be associated with atypical pneumonia more often than were the lower types of pneumococci.

The types of pneumococci harbored by patients with no pneumococcal respiratory disease were usually Types III, IV, or VI pneumococci, or those belonging to the types beyond VIII. In general, the sputums of patients suffering from non-pneumonic infections (acute and chronic bronchitis and lung abscess) contained pneumococci of this same group.

Table 2 is a comparison of the incidence of pneumococci, Types I through VIII, found in patients with pneumonia in various large cities of the United

TABLE II

Incidence of Pneumococci in Various Cities

	Boston		New York		San Francisco		Cincinnati		Washington	
	1929–1936 (Finland)		1928–1936 (Bullowa et al.)		1932–1935 (Kohl & Reitzel)		1935–1937 (Benjamin et al.)		1935–1938 (Dowling & Abernethy)	
	No.	%	No.	%	No.	%	No.	%	No.	%
I	709	24.3	725	23.7	138	42.8	156	32.1	87	25.0
II	319	10.9	256	8.4	39	12.1	52	10.8	13	3.9
III	439	15.0	297	9.7	27	8.5	50	10.3	31	8.8
IV	65	2.2	179	5.8	3	0.9	20	4.3	14	4.0
V	226	7.7	230	7.5	11*	3.4	47	9.7	21	6.0
VI	61	2.1	51	1.7	2	0.6	9	1.9	12	3.4
VII	164	6.8	194	6.3	14	4.3	43	8.9	25	7.1
VIII	235	8.1	225	7.3	8	2.4	30	6.2	28	8.2
XIV	76	2.6	87	2.8	4	1.2	6	1.2	7	2.0

* Including Types IIa and V.

States. The incidence of these types in Washington was very similar to that occurring in the other cities in the east, except that the percentage of Type II pneumonias was lower in this series than in studies coming from

cities farther north. This low incidence of Type II pneumonias was noted for each of the three years covered by the Washington study. The similarity between the type distribution of pneumococci in the eastern cities and that found in Cincinnati in the middle-west and San Francisco on the west coast, while close, is not as exact. Perhaps if the three studies which involve smaller groups of cases could be extended to include one thousand or more, as in the reports from Boston and New York, the figures would coincide even more closely.

Reliability of the Neufeld Test on Sputum

The Incidence of Positive Neufeld Reactions. The Neufeld test was performed on a total of 305 specimens of sputum. As shown in table 3, in 161 cases the same type was found by both the Neufeld and the mouse methods; or, if more than one type was found by either method, the predominant organism was found by both methods.

TABLE III

Reliability of the Neufeld Method

	How Confirmed			Total
	By Another Sputum	By Other Sources of Material	Not Confirmed	
Neufeld and mouse methods agree in one or more types.	27	15	119	161
Neufeld negative; mouse positive.	12	3	65	80
Neufeld positive; mouse negative.	1	0	1	2
Neufeld positive; mouse not done.	14	4	43	61
Neufeld one type; mouse another type.	0	0	1	1
				305

In 80 instances, no type was obtained by the Neufeld method, while from the mouse one, two, or even three types were isolated. In two cases the Neufeld test revealed one type while no pneumococcus could be obtained from the mouse. In a single case the Neufeld test revealed one type (Type XIII), while a different type (Type XXVIII) was obtained from the mouse.

It will be seen, therefore, that among 244 specimens of sputum typed by the Neufeld method and followed up by mouse typing, in 161 cases (66.0 per cent) the Neufeld test was confirmed, in 80 cases (32.8 per cent) the mouse test revealed a type while the Neufeld test did not, in two cases (0.8 per cent) a type was obtained by the Neufeld test while the mouse revealed

none, and in only one case where both tests were positive (0.4 per cent) were they contradictory in that a different type was obtained from each test.

The Accuracy of the Neufeld Reaction. The Neufeld test resulted in the finding of one or more types of pneumococci in 161 cases in which it was confirmed (for one or more of those types) by the mouse test; in one case in which it was contradicted by the mouse test; and in 18 cases in which the mouse test was not done on the same sputum but in which previous or subsequent specimens of sputum or of other exudates had revealed the same type of pneumococcus. Accordingly, in 180 cases in which the Neufeld test was confirmed by another test, it was found to be correct in 179 cases and (presumably) erroneous in one case. This would indicate that we found the test to be 99.4 per cent accurate when positive.

Discussion

The foregoing data show that in the District of Columbia the type distribution of pneumococci in carriers and in patients with pneumonia is quite similar to that found in other large cities from which reports have been published. The major discrepancy is the low incidence of pneumococcus Type II pneumonias. In this connection, it may be recalled that Type II pneumococci are the most typically pathogenic of all the pneumococci. They are the least often found in the throats of normal persons; they are sometimes responsible for epidemics of pneumonia [8]; they, in conjunction with Type I pneumonias, cause the classical picture of lobar pneumonia; and they are associated with as high a mortality as any other type. It is interesting to speculate as to whether this type might not be found in a decreasing portion of patients with pneumonia as one goes farther south. It is to be hoped that studies similar to the present one will soon be made in cities south of Washington.

In other respects the data in the present paper confirm previous findings elsewhere. Types I and II pneumococci have been shown to cause typical lobar pneumonia most frequently, less often atypical pneumonias. They are rarely found in the throats of normal persons and are practically never obtained from the sputum of patients suffering from bronchitis or lung abscess. Types III, IV and VI pneumococci and the Types above VIII offer a definite contrast. They seldom cause pneumonia with the typical clinical picture, whereas they are frequently found in the throats of normal persons and in the sputum of patients suffering from bronchitis and lung abscess. Pneumococci Types V, VII and VIII occupy a middle ground. They cause a higher percentage of bronchopneumonias than do Types I and II pneumococci, but not as high as do Types III, IV, VI and the "higher" types. Moreover, Types V, VII and VIII pneumococci are only slightly more often found in the throats of normal persons and in the discharges from bronchitides and lung abscesses than Types I and II pneumococci.

Specific serum therapy has been shown to be of value in the treatment of pneumonia caused by Types I, II, V, VII and VIII pneumococci. Its effect upon pneumonias caused by the other types of pneumococci remains to be proved. Now that rabbit serum is being made commercially available for the treatment of the pneumonias caused by all types of pneumococci, it is necessary for clinicians and public health officials in each community to know exactly how many cases of each type they may expect to find. According to the data presented here, at least 50 per cent of all pneumonias found in Washington can be treated by the use of specific serum.

Summary

1. The incidence of pneumococcus types found in cases of pneumonia, non-pneumonic respiratory disease, and in normal persons in Washington, D. C., has been presented.

2. The greatest percentage of pneumonias was caused by the following types of pneumococci in descending order of frequency: Types I, III, VIII, VII, V, IV, II and VI. These pneumococci, with the exception of Types III, IV and VI were rarely found in non-pneumonic respiratory infections or in the throats of normal persons.

3. The percentages of the various types found correspond, on the whole, to those found in similar studies from other cities in the north, mid-west and far west, except for a local scarcity in the percentage of Type II pneumococci.

4. The Neufeld method of sputum typing was found to give positive results in about two-thirds of all specimens examined. In about one-third of all cases, injection of the sputum into a white mouse was necessary to determine the type of pneumococcus present.

5. Although less delicate than the mouse method, the Neufeld method was 99.4 per cent accurate, when positive, as compared with the mouse method.

The technical work for this study was performed by Miss Margaret C. McMahon, Mrs. Marie T. Woodwell and Miss Emily A. M. Godfrey.

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TREATMENT OF HEART FAILURE*

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THE treatment of heart failure is too broad a subject to be comprehensively discussed in every detail in the brief space of one paper. It is manifestly necessary to touch upon much of the material in outline form and simply to state briefly the present status of the traditional forms of therapy. Newer methods and drugs that seem to be particularly interesting and promising will be more extensively commented upon. Personal observations or confirmations of the observations of others that seem particularly significant will be set forth. A report of some original or corroborative studies must be included in order to warrant publication. This will consist of a summary of work done during the past several years with the help of many associates, but particularly that of Dr. George M. Decherd, Jr.

The delineation of personally directed investigations is reserved for the body and the end of the paper, and may perhaps thus receive undue emphasis. The studies of the chemical nature of heart failure have been discussed in a previous communication.[1] The therapeutic approaches suggested by this work have not yet advanced to a point where they rate more than being mentioned in a conservative paper. Our conclusions as to the mechanisms by which the two main types of diuretics, the xanthines and the mercurials, accomplish their results will be presented. Observations on the newer and better combinations of drugs for the elimination of edema fluids will, however, be reported upon somewhat more in detail.

PREVENTIVE THERAPY

The treatment of heart failure should be taken into consideration upon the discovery of evidences of potential heart disease or myocardial damage. The pronouncement of the diagnosis is best withheld. Steps, however, should be taken immediately to work out a plan of life that will protect asymptomatic cardiac patients. The hope is to postpone as long as possible the almost inevitable heart failure. The damaged heart, if spared every unnecessary strain, may carry on for years.

The removal of the *etiological factor* even when it is apparent is only rarely possible. Treatment directed against the causative process is nevertheless in order in the hope that the progress of the condition may be arrested. Chronic syphilis should be treated most carefully and persistently in the presence of syphilitic aortic disease. The milder antisyphilitic drugs should be continued for long periods of time. Bismuth, mercury and

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iodides if administered year in and year out will accomplish almost as much as neoarsphenamine and are much less dangerous.

Rheumatic fever is almost an unknown quantity bacteriologically. Rest in bed for many months is justified treatment. The use of daily rations of salicylates if well tolerated for as long as two years after an acute attack has only empirical support. The removal of infected tonsils is of disputed value.

Hyperthyroidism, of course, may be controlled by medical and surgical means and the cardiac damage may be prevented although the original condition is not amenable to prophylaxis.

The hypertensive arterial cardiorenal disorders are usually insidious in their onset and well developed when discovered. Many factors in the genesis, pathological physiology and progress of hyperpiesia are fairly well understood. There is no certain method for permanently lowering blood pressure to normal levels. Management, however, may accomplish much in prevention or in checking the speed of progress of the degenerative changes. A moderately low protein, low fat, salt poor, high calcium and high vitamin diet may contribute to some extent toward this end. Such dietary restrictions are indispensable in patients with chronic nephritis. The stemming of the tide in these disorders and in premature degenerative arterial disease are the problems of modern preventive medicine.

Some Fundamental Pathophysiological Considerations

Inasmuch as the causative factors of heart disease are still for the most part beyond control, we must concentrate our efforts on the control of those *precipitating factors* that lead toward or are important in the development of heart failure. Over-exertion must be avoided. Acute and chronic infections and increased metabolic rate are generally recognized as factors which would contribute to further cardiac damage and call for careful management. Unfortunately little can be done to prevent the sudden or slow development of obstructive lesions in the coronary system, or cardiac hypertrophy and enlargement. The advance of sclerosis of the coronary bed and increase of cardiac hypertrophy are progressive processes which go on insidiously, but may be significantly slowed by proper management. Chronic myocardial anoxemia would account for the chemical abnormalities that have been noted in the hearts of patients who have died of heart failure.[1] Hypertrophy of heart muscle cells undoubtedly interferes with the circulation and impairs the oxygenation and nutrition of the cells.[2] Oxygen administration may be of considerable help.

Experimental Attempts at Physiological Adjustments

Consideration of the chemical changes such as have been outlined in the previous papers [1] should aid in the understanding of the nature of the degenerative processes that are going on silently as the heart disease progresses.

The further investigation and absolute definition of these changes eventually may contribute something more in the way of a rational myocardial protective therapeutic regime. The electrolyte changes in the blood stream and the blood serum protein losses [1] and chemical changes in the tissues are apparently not of first importance. The phosphocreatine disturbances in the heart muscle are of the greatest significance. Measures that would tend to conserve phosphocreatine, total creatine and phosphorus would tend to postpone the evil day of heart failure.

Aminoacids as alanine, glycocoll and glycocyamine and arginine have been suggested to stem the loss of creatine and of phosphorus and presumably of phosphocreatine in the heart muscle. The suggestions have come from theoretical considerations and from perfusion experiments with solutions containing the specific substances. Our own experiments were not as successful as those of the Englishmen at Oxford. We have found, however, that the amino-acid glycocoll administered by mouth in one gram doses, even in the presence of extreme heart failure, will often relieve the sense of exhaustion that such patients experience and tide the patient over a crisis. Glycocoll seems to act beneficially even after coronary thrombosis with extensive myocardial infarction. This has not yet been conclusively demonstrated to be anything more than a specific dynamic effect of the aminoacids. Glycocoll cannot, therefore, as yet be recommended for general use.

Digitalis in adequate dosage as shown by our experimental studies [1n] and some clinical studies, has a tendency to conserve and apparently in some instances to increase the total creatinine content of the heart muscle.[3] Furthermore, the animals whose hearts have been put under the stress of traumatic valvular lesions and digitalized live longer and develop less cardiac enlargement.[1f] Digitalized rabbits subjected to sudden myocardial stretching from injections of volumes of 6 per cent or 12 per cent buffered acacia solution equal to the blood volume of the animal had a much lower mortality rate and developed on the average statistically lesser grades of hypertrophy.[1] Our hypertrophy limiting results with digitalization have not, however, been nearly so striking as those of Cloetta [3] upon the basis of which Christian [4] recommended the regular use of digitalis to limit cardiac hypertrophy. We have added the suggestive chemical evidence of the possible beneficial creatine-conserving action of digitalis.[19] There may be some question raised as to the validity of the established basis for the routine administration of digitalis as a prophylactic against advancing hypertrophy and failure in patients with potential or probable asymptomatic heart disease. Nevertheless, further clinical observations of the effect of years of digitalization seem to be in order.

Increasing the Oxygenation of the Heart Muscle

Oxygen is evidently the most essential element, the curtailment of which is most threatening to the maintenance of adequate heart muscle

function.[5] Unfortunately we are not able with ease to bring oxygen directly to the heart muscle cells. Indirectly we have long used the xanthines, particularly aminophylline, with the hope that coronary vasodilatation and consequently better myocardial oxygenation would be accomplished. An augmentation of the deficient blood supply to a heart should contribute to more nearly normal oxygenation and more adequate metabolism and would account for observed clinical improvement. The question has been raised as to whether the xanthines really act as they have been thought to act, as vasodilators. Recent careful perfusion experiments have failed to show any increase in coronary flow in the isolated heart after the use of xanthines. Gold and his coworkers[6] have failed to obtain clinical evidence of any beneficial effect of xanthines in angina pectoris. These conclusions are contrary to the earlier findings of Fred Smith and the results of Friedman, Resnik, Calhoun and Harrison.[5]

I still believe that something more than psychotherapeutic results is obtained with xanthines if the dosage is adequate. The report that aminophylline was ineffectual has, however, cast some doubt upon the logic of its daily use in asymptomatic heart disease as well as in those with symptoms of coronary or myocardial insufficiency. The Council on Pharmacy and Chemistry of the American Medical Association now accepts xanthines as diuretics and myocardial stimulants but not as vasodilators.

General Considerations

Treatment, after the appearance of symptoms of heart failure, depends upon the type of heart failure. The treatment of the anginal type of heart failure will not be further discussed.

In the milder forms of congestive failure, the patient may present nothing more than easy fatigability, weakness and physical exhaustion, without or with increasing breathlessness. The indications are for the temporary alleviation of the physical and consequently the circulatory load, with a definite decrease in the demand for oxygen or for a *lowering of the basal metabolism.* Small frequent feedings of a well balanced diet, low in fats, high in vitamins, gelatin, and carbohydrates, unless there is diabetes mellitus, and adequate in proteins of good biological character is essential in an attempt to maintain osmotic pressures and homeostasis.

The minimal demands upon the heart muscle under a low basal metabolic status may be attained by subjecting the patient to partial *starvation* at *rest* in bed. Semistarvation and restriction of fluid and salt intake, and of physical activity to the limits established by careful observation of the patient's reaction, may be sufficient to keep borderline patients in circulatory equilibrium for long periods of time. The dietetic and physical management is usually supplemented by drug therapy in the form of small daily doses of digitalis or large doses of a xanthine preparation.

The patient is instructed *to avoid sudden stresses and strains,* to lower his body weight to somewhat below his standard weight and maintain it at that level; and to respect respiratory infections. Usually sooner or later as age advances, in spite of faithful abidence by restriction, trouble begins. Breathlessness comes on even with restricted activity. Periods of complete mental and physical rest, digitalization and sometimes the use of diuretics are necessary.

Emergency Therapy

Emergency measures are demanded in *acute congestive failure.* In acute *engorgement,* venesection or other methods of blood letting may be necessary to save life. The presence of a *serious cardiac mechanism disorder,* a paroxysmal auricular fibrillation or flutter, tachycardia, bradycardia or heart block which has precipitated or contributed to congestive failure calls for immediate specific measures for the control of the disorder.

The anoxemia of acute pulmonary edema or of pulmonary embolism or of coronary thrombosis calls for forced concentrated *oxygen* atmosphere to tide the patient through the crisis. Collections of transudated edema fluid in the body cavities, or even in the pericardium itself, acting as a handicap to the efficiency of respiration or to the movement of the diaphragm, or tamponading the heart, should be removed.

The *chronic type of heart failure* is by far the more common condition and requires the most persistent efforts and careful general management. An attitude of hopefulness and optimism is necessary in the handling of these conditions. In my experience there has been abundant justification for this psychotherapeutic measure. Many patients who have suffered from failure have been relieved of the distressing symptoms, made comfortable, happy and useful and practically rehabilitated by adequate treatment and judicious advice. The physician must be equipped and ready to change his methods and his therapeutic agents and to employ other preparations when the effects of those that he is using are no longer satisfactory.

Some Details of Routine Management

The potential or probable and asymptomatic heart disease patient should be given some protective and general dietary supervision.

Rest is perhaps the most important single therapeutic measure that can be instituted for the relief of the patient with the failing heart and circulatory embarrassment. Rest, however, to be effective must be complete, mental and physical, and must be prolonged. No detail that will contribute to the patient's comfort should be omitted. He should be supported in Fowler's position with a rather firm back rest and hard pillows. When possible a cardiac table as well as a cardiac bed should be provided. Evacuation of the bowels should be accomplished without any strain, preferably with the use of a bedpan slipped passively under the patient. If this is a

great ordeal for the patient it is sometimes less exhausting to have a commode, built to the level of the bed, upon which the patient may be gently lifted or shifted, without any effort on his part. It must be remembered that the lifting of the body weight even by the musculature of the arms is a considerable physical exertion. Changing of position in the bed should be done by the nurse and the patient spared every effort.

In the most severe stages of heart failure when a patient is dyspneic and orthopneic it is highly desirable to ensure rest by the use of sedatives. Paullin [7] has recently called attention to the fact that morphine sulphate given hypodermically in ¼ to ½ grain doses is one of the most valuable drugs used in the treatment of heart failure. As Houston [8] has suggested, the sedative effect of morphine upon the respiratory center spares the patient the great muscular exertion of the usual overactivity of the respiratory mechanism in congestive failure. Morphine breaks the vicious circle that exhausts the patient, allays anxiety, relieves the strain and pain and ensures sleep. Dilaudid probably has some advantages over morphine sulphate in the prolonged treatment of cardiac invalids. It is apparently equally effective in the control of respiratory distress in considerably smaller dosage, namely 1/64 to 1/32 of a grain (1 to 2 mg.). The effect on the respiratory center as revealed by the rate must be carefully noted for in an occasional susceptible individual, a temporary suspension of breathing may occur and requires artificial respiration. The chief argument in favor of dilaudid, however, is the fact that it is not constipating, and that its withdrawal is not disturbing to the patient.

Diet. In general, in the presence of heart failure there should be some restriction in the total food taken each day and at each meal. There should be no large meal, but five or six small feedings so spaced as to allay hunger. At the same time, spread the work of digestion over periods of hours. The amount of fluid taken with each meal should be reduced to a minimum and taken slowly. Overfilling of the stomach and consequent mechanical embarrassment of the heart action is to be avoided.

A fairly balanced diet with a total caloric value between 1,200 and 1,500 made up of foods that have a tendency to yield an acid ash is most desirable. Sodium chloride should not be added to the food. The fluid intake for 24 hours should be limited to six glasses or 1,400 c.c.

The foods selected should be easily digestible dairy products, particularly milk and eggs. In the absence of diabetic tendencies carbohydrates with a high sugar content seem to be desirable.

One must not neglect the need for proteins of good biological character. Delicate meats, as chicken and fish and liver, milk and egg albumin in sufficient quantity must be supplied to meet the metabolic demands and in an attempt to maintain the blood proteins at a normal level. In one of my earlier chemical studies [1b] I demonstrated the tendency toward abnormally low serum protein levels in patients with heart failure. Proteins are also

useful in furnishing urea and mineral electrolytes and in promoting optimal urinary secretion.

The Treatment of Edema

In the presence of extensive and refractory edema due to congestive failure, as nearly a salt free dietary as possible is necessary; and a flow fluid intake will also usually help to restore a normal water metabolism. The Karrell diet of four glasses of milk of 200 c.c. each, one every four hours and nothing else, is quite poorly balanced and inadequate and should be continued only for a few days to a week at the most. Carbohydrate and protein should be gradually added. This régime is usually sufficient to inaugurate a diuresis and once started it may continue. Other measures may be used to contribute to the maintenance of the diuresis.

High potassium containing foods as potatoes and bananas may be substituted for the milk. Later on the continental diet of unpeeled raw fruit and vegetables with only the natural juices for fluids, a total of 1,500 gm., may be tried. Skimmed milk, eggs and cereals must eventually be added to balance the diet. Any foods that cause distention or foods to which the patient has reacted abnormally should be eliminated from the diet.

Acid Salts. The administration of acid salts, as ammonium nitrate, ammonium chloride, potassium chloride or calcium chloride in doses of 15 to 30 gr. (1 to 2 gm.) three times a day may produce a relative acidosis and inaugurate or continue diuresis. Barker and his group[9] in Chicago have reported good results from the use of potassium in effecting the replacement of sodium. I use acid salts, ammonium and potassium chloride, usually in conjunction with other diuretics, particularly the organic mercurials, to augment the effect of these preparations as Keith and his collaborators[10] advocated. The shift in the sodium and chloride ion relationship in the relatively acidotic state and the decrease in the alkaline reserve and the increase in the permeability of the capillary walls and in the osmotic pressure of the blood plasma all favor the drawing of the fluids from the tissues. Ammonia is changed to urea leaving the chloride ion to combine with the fixed bases of the plasma and tissues.

Urea, itself, may be administered in doses as large as (½ to 1 ounce) 10 to 30 gm. a day if there is no evidence of impairment of renal function or retention of nitrogen waste products and this may be very effective in controlling the chronic types of dropsical states.

The antiquated saline catharsis method or a modification of it, consisting in the use of concentrated salts for the removal of fluid in the body, has been found to be far too drastic and has fallen into disrepute. Hypertonic enemas are no longer in use; in fact they are no longer considered to be innocuous. Mineral oil and agar agar emulsion with or without cascara to encourage regular bowel movements and make unnecessary any straining at the stool must be a part of the sane management in such cases.

Digitalis. Digitalis is the drug of choice in patients with heart disease. It is a cardiac tonic that relieves breathlessness and edema. It acts most dramatically in patients with auricular fibrillation. However, most edemas of congestive heart failure disappear under adequate digitalization whether the cardiac mechanism is regular or irregular, as Christian demonstrated many years ago.[11] There is now abundant evidence that digitalis acts primarily on the heart muscle in such cases. Dock and Tainter [11a] have shown that there is a secondary but also important action of the drug upon the peripheral circulation.

In the presence of auricular fibrillation, digitalization, through vagus stimulation, depresses the conduction and decreases sharply the ventricular rate and eliminates the pulsus deficit. Occasionally the circus mechanism may stop spontaneously as a result of the improvement of the circulatory equilibrium and in spite of the myocardial blocking effects of digitalis. Digitalization improves considerably the general circulation, particularly that in the brain. Cheyne-Stokes breathing and paroxysmal nocturnal dyspnea may be entirely relieved. Similar results may be obtained by morphine or by the intravenous use of aminophylline which apparently favorably effects the cerebral circulation and the respiratory center as Nathanson has so clearly shown. Most patients require 1 cat unit per 4 kg. or for each 10 pounds of body weight for digitalization. This may be accomplished with the standard powdered leaf of digitalis, pills, capsules or the tincture. Using the rapid oral method I give 4 pills (6 gr.) or 4 cat units every 4 hours for two doses, then 4 pills every 6 hours for two doses, then one pill every 6 hours to nausea, vomiting, diarrhea, xanthophobia or block. The slower, and slightly safer method is to use 2 pills (3 gr.) every 4 hours for 10 doses, then one pill every 6 hours until symptoms appear. New digitalis preparations are appearing on the market and demand careful clinical assay.

More highly concentrated purified crystalline and amorphous preparations of digitalis glucosides have been introduced from time to time. These are described in the booklet, "The Cardiac Glucosides" by Arthur Stoll. The extensive bibliography of this book should be consulted for references that follow. In 1869, Nativelle described "digitaline crystallisée" as a crystalline insoluble very active principle of digitalis. This was probably digitoxin. It was not introduced until the pharmacologic work of Cloetta in 1920, which established the dose of 0.1 mg. (1/600 gr.) as equal to 0.1 gm. (1½ gr.) of the standard powdered leaf or 1 c.c. of the standard tincture of digitalis.

The gitalin fraction or amorphous gitalin isolated by Kraft and studied by Straub, introduced as verodigen and now called gitalin amorphous, is a highly purified cardiac glucoside isolated from digitalis purpurea. It is apparently rapidly and completely absorbed in the gastrointestinal tract. 0.25 mg., 1/240 grain, produces about the same clinical effect as 1½ grains of powdered leaf digitalis. The clinical dose necessary is small and has

therapeutically the desirable action of digitalis. The optimal effect is accomplished by 2.5 mg., 1/16 to 1/10 of a grain in a period of five to six days. Gitalin amorphous apparently retains its action without any change in potency or deterioration over periods as long as two years, according to Stroud and his co-workers.

Southeastern European, Balkan or Austrian *digitalis lanata* has yielded a number of very cardiac glycosides, according to German, French, Swiss. and English pharmacologists. S. Smith not only isolated digitoxin and gitoxin from *digitalis lanata* but also a new crystalline glucoside *digoxin* which cannot be obtained from digitalis purpurea. Digoxin was found to be a stable crystalline substance of known definite chemical composition

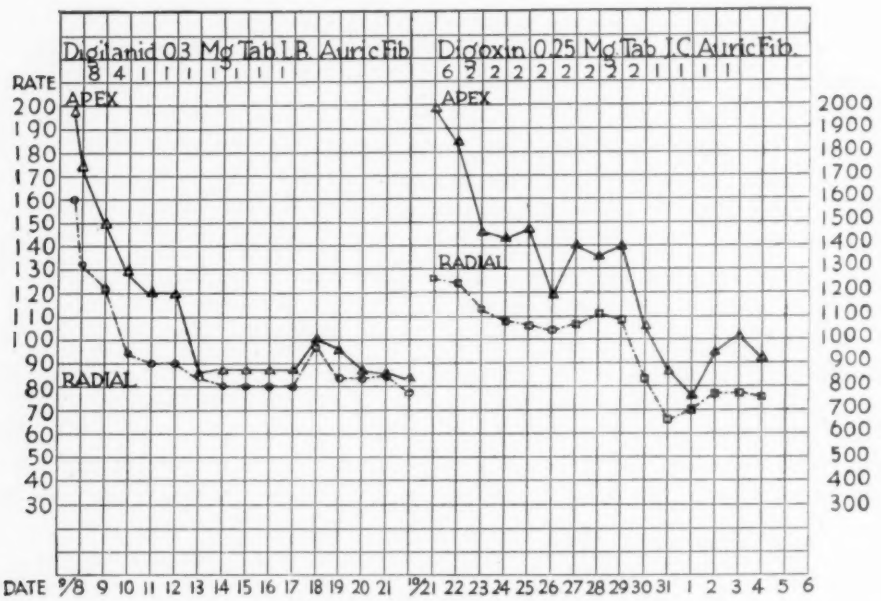

FIG. 1. Effects of digilanid and digoxin given by mouth on the heart and the pulse rates in a patient with auricular fibrillation.

(C_{41} H_{64} O_{14}). Digoxin administered clinically was found to be effective even in very small doses of 0.25 mg. (1.240 grain) equal to 0.1 gm. (1.5 gr.) of powdered leaf digitalis. It is promptly and fairly completely absorbed. Digitalization can be accomplished with 1 to 1.5 mg. (1/60 to 1/40 grains). Intravenously the dose of 0.75 mg. to 1 mg. seems sufficient. Digoxin is very rapidly eliminated from the body and therefore the daily dosage of 1/3 the digitalizing dose, namely 0.5 mg. (1/120 grain), is necessary to maintain a digitalizing effect. The response to the intravenous dose of digoxin is evident within an hour and usually complete within two hours, but by mouth it takes about two hours before the effect is very definitely demonstrable and four hours before completion. The value of

the digoxin in terms of cat units is considered unnecessary by the manufacturers, since it is a chemical entity, the dosage of which can be accurately controlled by weighing. They argue, probably justly, that weighed digoxin is far more uniform than a preparation standardized by the cat method of assaying. Nevertheless, the cat unit value should be established and stated on every product, in order to prevent poisonings in the hands of some who are accustomed to considering one tablet of a cardiac glucoside to be equivalent of 1½ gr. of the standard powdered leaf of digitalis, or one cat unit, as is so often the case with most other digitalis tablets.

Lewis [12a] has accepted digoxin in the place of the more variable and less safe strophanthin G. or ouabaine. Wayne [12b] reported favorably on the clinical efficiency of digoxin. Stroud's [12c] results with digoxin have been corroborative and my own limited experiences have been similar.

Digilanid glucosides extracted by Stoll and Kreis from the digitalis lanata were found by them to consist of isomorphic crystalline complexes made up of three chemically distinct substances. Lanata glucosides lanatids, or digilanids A, B and C, were found to make up A 47 per cent, B 17 per cent and C 36 per cent of the isomorphic crystalline complex respectively. By careful chemical analysis, hydrolysis and deactylation, Stoll and Kreis found digilanids A and B to yield identical substances to purpurea glucosides A and B. Purpurea digitalis, however, did not contain anything comparable to the important and most active digilanid C and its derivative digoxin. The isomorphic crystalline complex was found to be chemically pure and stable, insuring a constant relation between the therapeutic and toxic effect. Rapid absorption and prompt action, but particularly the persistence of its effect, are advantages in favor of this preparation. The amount of digilanid required for digitalization is about 1.0 mg. (1/60 grain), each tablet of 2/3 mg. (1/100 grain) being equivalent to 1.0 gm. (1½ grains) of the standard powdered leaf or one cat unit. We have had good results from this preparation. The maintenance dose is 1 1/3 mg. or 1/50 grain per day.

Digoxin and digilanid have been found to be so promptly, uniformly and completely effective that they have practically displaced other intravenous preparations. In auricular fibrillation they cause dramatic slowing of the ventricular action. These preparations also produce profuse diuresis in patients with edema just as the other digitalis preparations in adequate dosage are known to do.

In view of the creatine-conserving effect and possible hypertrophy-restraining action of digitalis, the question of whether prolonged digitalization in maintenance doses over periods of years produces any undesirable toxic changes in the heart must be opened again for debate. Bauer and Fromberg, using excessive doses of digitalis, apparently produced irreversible histological myocardial damage. Trendelenburg showed that the Starling heart-lung preparation responded to digitalis only after the myocardium had been overwhelmed. Edens has insisted that only the hypertrophic and failing heart responds to therapeutic doses of digitalis in characteristic

fashion. Experimentally, hypertrophied hearts were found by Weese to be increasingly sensitive to digitalis.

The heart muscle, especially when damaged, has a specific affinity for glucosides, and absorbs proportionately large amounts of these substances. Fixation of the glucosides in the heart muscle is responsible for the cumulative effect of digitalis administration. This is desirable and reversible when accomplished by small doses. The effect of digitoxin and digoxin may be considered irreversible, but continued irrigation will usually revive

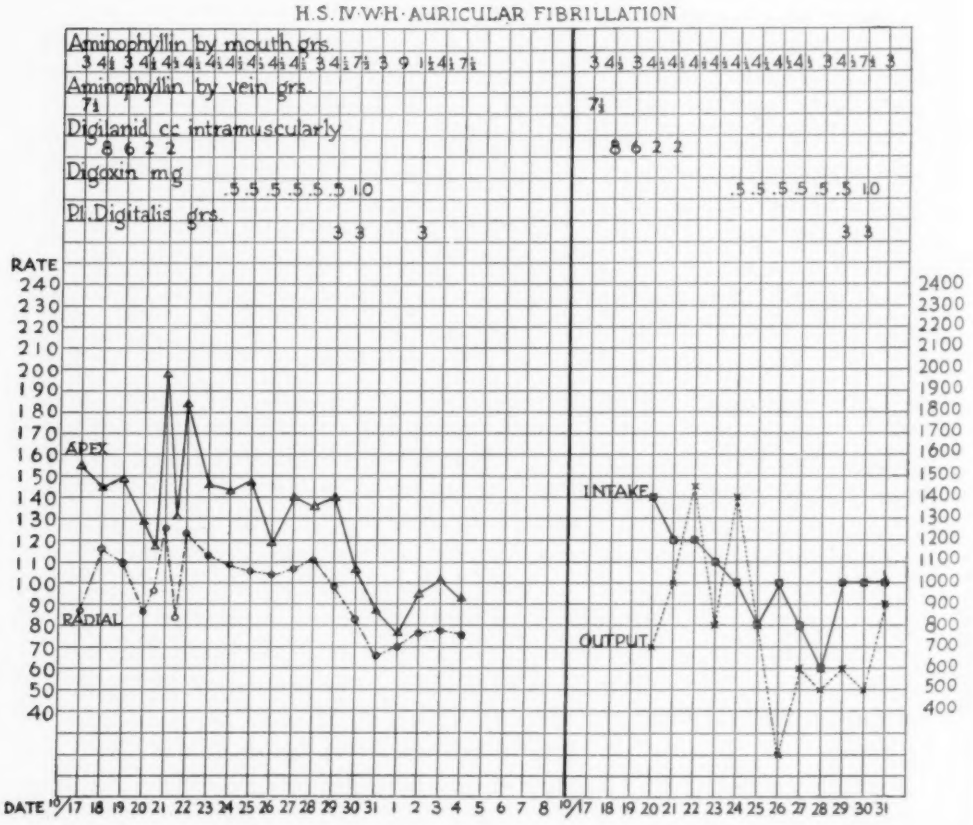

FIG. 2. Effects of digilanid and of digoxin on heart and pulse rate and fluid output in a patient with auricular fibrillation in chronic congestive heart failure and edema.

hearts, even when they have been stopped by such powerful glucosides. Digilanid C effect is more easily reversed. Digilanid B, Scillaren A, Strophanthin G, and gitoxin are most easily washed out.

Our clinical and experimental studies seemed to show a tendency to retention of creatine as the result of digitalization, which would be interpreted as a desirable effect. Our experimental studies have also revealed a tendency to restriction of hypertrophy by digitalization. We are beginning

to feel that perhaps there may be justification for the prolonged use of digitalis for this purpose.

The myocardial creatine-sparing value of digitalis noted in our experiments may be an argument for reconsidering the question of digitalization in pneumonia. The low levels of creatine in the heart muscle of those patients who had died of heart failure, but particularly those who had died of pneumonias, are a basis for reopening this discussion. The use of digitalis in pneumonia at the present time is unceremoniously condemned on statistically questionable grounds.

The Xanthines or Purines. Caffeine, theobromine and theophylline, members of the vegetable purine or xanthine group of diuretics, for some time past, have been widely used in the treatment of congestive heart failure. The theobromine and theophylline combinations have been accepted, up until recently, as effective in anginal failure. Caffeine, because of its cerebral stimulating effect is not routinely used in the treatment of chronic cardiac patients but is occasionally administered in the form of caffeine sodium benzoate as a temporary circulatory stimulant.

Theobromine preparations, particularly theobromine sodium salicylate "Diuretin," was one of the first of this group to be introduced as a renal diuretic in patients with edema. It is still quite widely used, particularly in combination with calcium to enhance its diuretic properties, or with a barbiturate as a sedative.

Theophylline derivatives, "Theocin," theophylline sodium salicylate, or calcium salicylate, theophylline with ethylene diamine, or with methyl glucamine have been, perhaps, most widely used as coronary vaso-dilator cardiac stimulant and diuretic agents. Smith [5] and his coworkers found theophylline to be more effective than any other xanthine in increasing the coronary flow in the experimentally isolated heart. Confirmatory clinical evidence of the value of these drugs was brought forth by Friedman, Resnik, Calhoun and Harrison [5] in a study of cardiac output and vital capacity of patients following treatment orally with theophylline salts, particularly aminophylline.

Aminophylline by mouth often greatly relieves paroxysmal dyspnea and sometimes causes attacks to disappear entirely for a time. I have found it worthwhile to use aminophylline in this way before resorting to its use intravenously or to digitalization or routine injections of morphine. Theophylline apparently produces myocardial stimulation, probably an increased coronary and cerebral blood flow and the removal of minimal amounts of edema. Latent edema, even though not demonstrable, may be significant.

In all of our original diuretic experiments in which we studied the effect of xanthines one day and of the mercurials the next day in the same patients it was frequently noted that there was a very definite augmentation of diuresis. We, therefore, tried various combinations of theophylline and mercurials and found that we could use much smaller doses of the mercurials and found that 1 c.c. of 10 per cent solution of salyrgan was as effective as 2 c.c. intravenously if we added 0.26 gm. (4 grains) of aminophylline. The

combination seemed to be less irritating and less toxic as well as more efficient. A mixture of a xanthine and a mercurial seemed to be rational. The supplementary actions of the two were totally different in effect and resulted in a definite increase of the urinary flow.

Our studies utilizing the creatinine clearances of Rehberg following the intravenous use of theophylline in patients with anasarca or generalized edema of congestive heart failure seemed to show that the theophylline accomplishes its diuresis primarily by increasing the glomerular filtration and affecting the reabsorption only slightly in the way of depression. The glomerular filtration may be considered as evidence of the vasodilation and

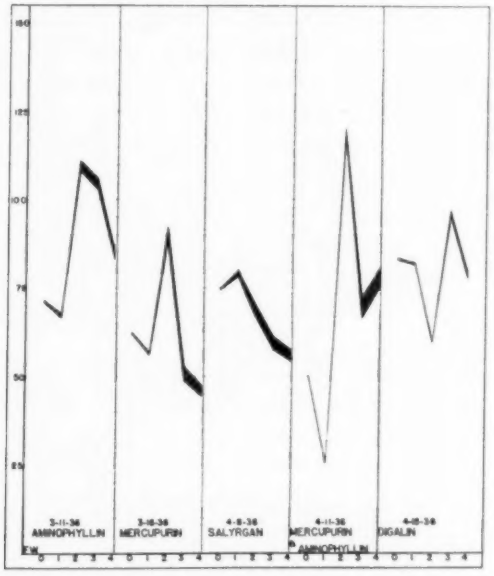

FIG. 3. Representation of glomerular filtration (upper edge) and tubular reabsorption (lower edge) as determined by creatinine clearance studies after various intravenous injections. Note the increased filtration with the xanthines and decreased reabsorption with the mercurials and combination effects.

increased blood flow to the kidneys. Edema interferes with adequate circulation and efficient oxygenation of water-logged tissue as well as adding a further burden of increased body weight. It is therefore desirable to remove edema as promptly as possible.

Mercurial Diuretics. Organic mercurial salts were introduced at first for intravenous use in the treatment of syphilis. Novasurol, one of the first of these preparations to be used with clinical benefit, was noted upon injection into patients with syphilitic aortic insufficiency and congestive failure to produce profound diuresis. Novasurol, however, was found to cause undesired reactions in certain individuals and less toxic organic mercurial salts were therefore sought. Merbaphen, mersalyl or salyrgan was introduced

and found to be much less toxic than the original preparation and just as efficient. In our creatinine clearance studies on the effect following the intravenous injection of salyrgan into patients with congestive heart failure and edema, we found that in contrast to theophylline the mercurials produced a marked decrease in tubular reabsorption and thereby accomplished the dramatic outpouring of edema fluids.

We have since learned that Foldy in experimenting with various new organic mercurial salts added a small amount of acid theophylline solution in order to neutralize the irritating alkalinity of new highly acid organic

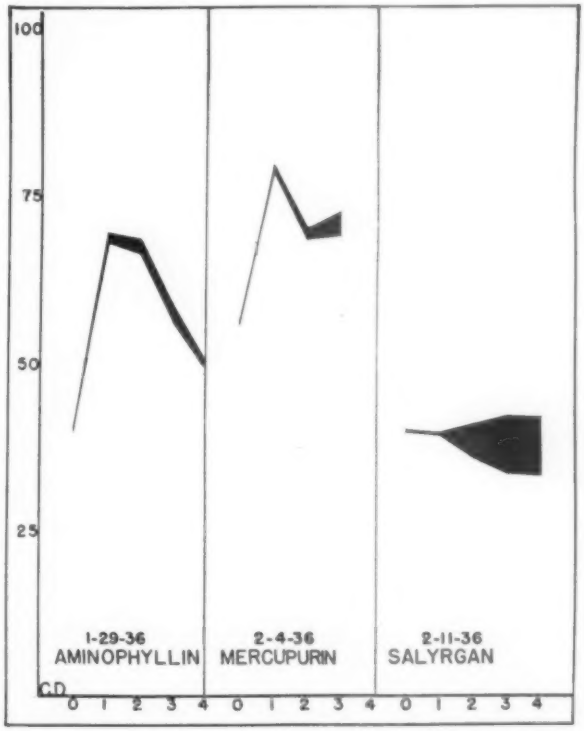

FIG. 4. Representation of glomerular filtration (upper edge) and tubular reabsorption (lower edge) as determined by creatinine clearance studies after various intravenous injections. Note the increased filtration with the xanthines and decreased reabsorption with the mercurials and combination effects.

sodium salt of mercury. The addition of the theophylline was found not only to make the combination non-irritating but also definitely to augment the action of the mercurial as diuretic in experimental animals.

A combination organic mercurial and theophylline diuretic under the trade name Novurit was put to clinical trial abroad as Novurit and was enthusiastically championed in the Hungarian publications of v. Issekutz and v. Vegh.[15] It was introduced in this country as mercupurin, described as a sodium salt of trimethylcyclopentane-dicarboxylicacid-methoxy-mercury-

allylamide-theophylline, containing theophylline 3.5 per cent combined and 1.5 per cent free, making a total of 21.5 per cent of mercury. DeGraff, Nadler and Batterman [16] who have studied the preparation extensively have stated that the 13.5 per cent aqueous solution of mercupurin contained 29.1 per cent of mercury by weight so that 1 c.c. contained 0.0393 gram of mercury, comparing thus favorably with salyrgan containing 39.5 per cent mercury by weight and 1 c.c. of the same 10 per cent solution containing 0.0396 gm. of mercury about the same amount.

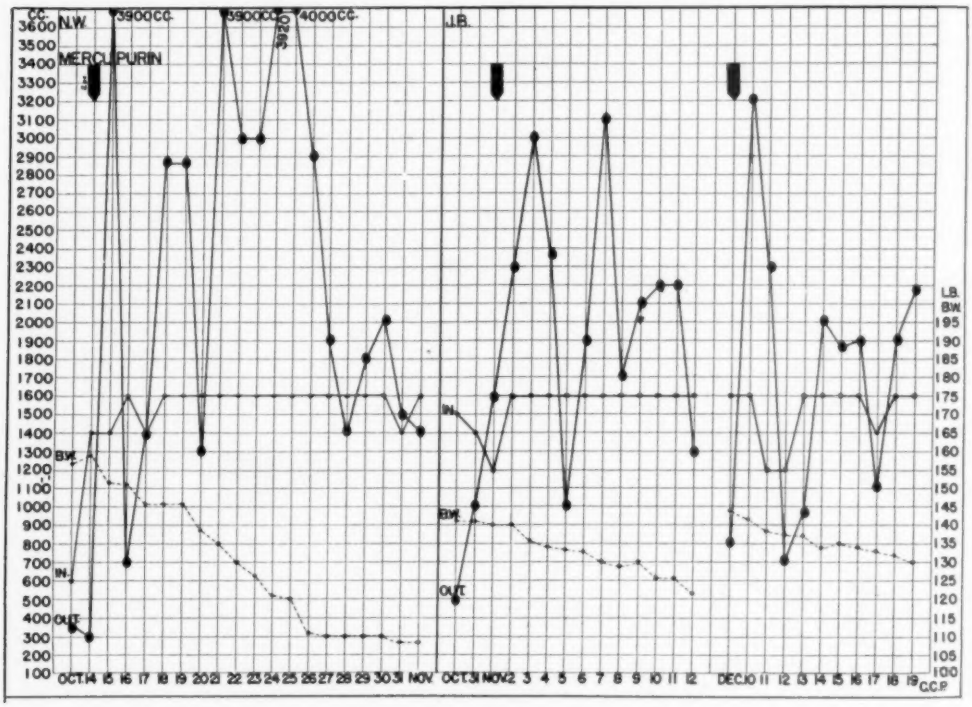

FIG. 5. Fluid output and intake and body weight levels in two edematous patients (N. W. and J. B.), who were given mercupurin intravenously.

The new preparation is said to differ from salyrgan only in that camphoric acid is substituted for salicylic acid. This substitution is said to have made the preparation about half as toxic as well as more effective. The mercurated camphoric acid without the alkaline theophylline added made up in cocoa butter has been distributed as a mercurial diuretic suppository "Mercurin" for rectal administration.

In the clinical studies of DeGraff and his co-workers [16] in 20 edematous patients under carefully controlled conditions with particular respect to the body weight changes, the combination preparation, mercupurin, was given intravenously and was found to produce distinctly better diuresis than the

intravenous injections of the mercurated camphoric acid without the theophylline added. These investigators, therefore, concluded that theophylline contributed definitely to the effectiveness of the mercurial preparations and to the superiority of the new mercurials with theophylline added. They, furthermore, commented on the absence of local reactions and of general toxic mercurial reactions from the intravenous administration of nearly 100 injections. Steurer and Wolpaw [17] reported a very small series of 35 injections and came to conclusions which corroborated those previously made.

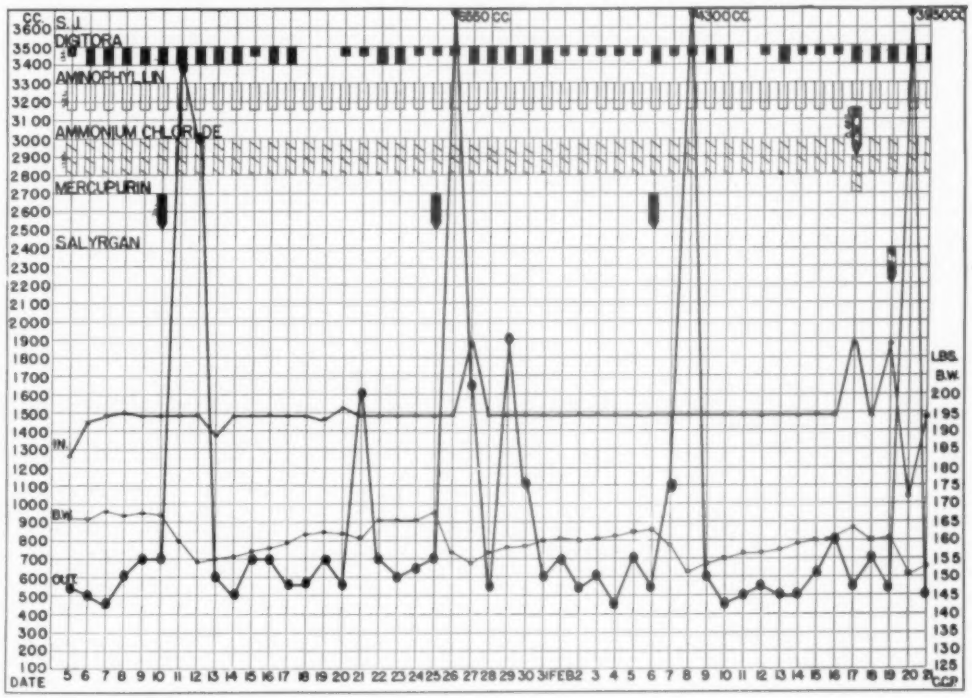

FIG. 6. Fluid output and intake and body weight levels in S. J. in chronic congestive failure treated with constant digitalization, acid salt therapy and aminophylline and fortnightly intravenous injections of mercupurin and lastly aminophylline IV followed by salyrgan.

In England, Parkinson and Thomson [18] have conducted clinical studies of the comparative values of mercupurin and salyrgan intravenously and mercurin administered in suppositories with and without the use of an acid salt. They found that the newer preparations are rather more efficient. Fulton and associates [19] recently reported that the diureses following mercurin suppositories were quite comparable with those obtained by parenterally administered mercurial salts.

Our Clinical Studies

Comparative clinical studies of the efficacy of the intravenous administration of mercurials and combinations of diuretics, salyrgan and aminophylline, mercupurin as well as theophylline and digitalis preparations for the same purpose, have been carried out in the wards of the John Sealy Hospital for the past four years. During the second year of our study mercurin suppositories and more recently salyrgan-theophylline injections of 2 c.c. aqueous solution containing 10 per cent salyrgan and 5 per cent theophylline have been under clinical investigation. Our data concern the results of some 600, three day studies on 188 patients with edema, all of whom have been under observation under standard conditions during a preliminary five day rest in bed on a constant intake of 1,400 c.c. of fluid and a standard low protein, salt poor diet.

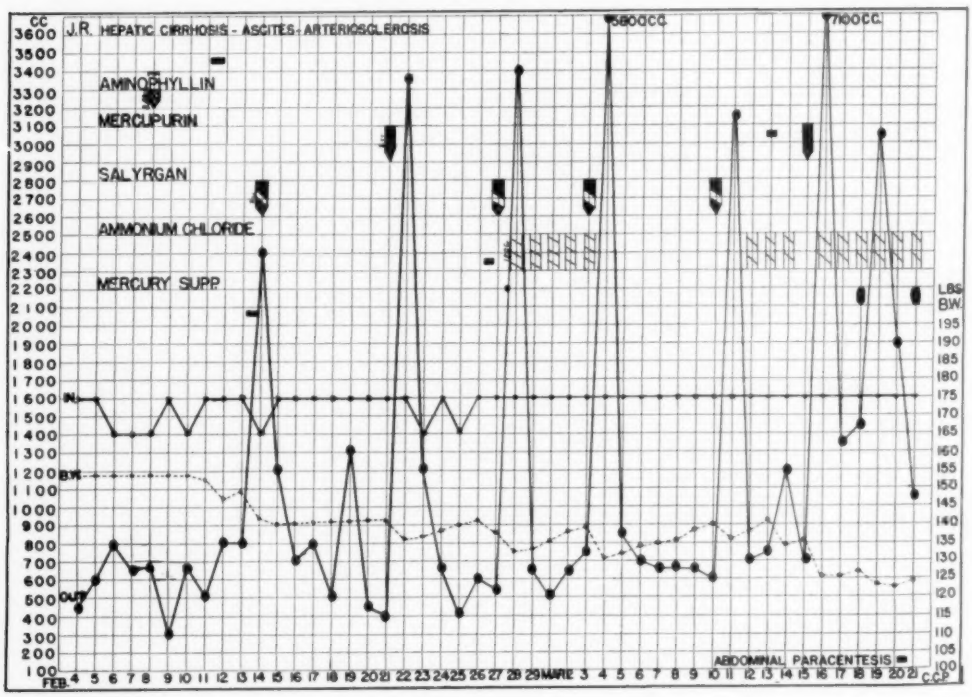

FIG. 7. Diuresis chart of a patient (J. R.) with hepatic (?) cardiac cirrhosis and congestive failure treated with various diuretics and finally with mercurin suppositories.

Only seven of these patients suffered primarily from the effects of cirrhosis of the liver (three of these had syphilitic cirrhosis), two had definitely advanced cardiac cirrhosis. The great majority of cases presented evidences of organic heart disease of one type or another for the most part hypertensive heart disease or syphilitic aortitis with congestive failure in various stages and of varying degree. In these, 366 injections of mer-

cupurin in doses of 2 c.c. of a 13.5 per cent solution were given intravenously alternately with 125 injections of salyrgan given in 2 c.c. doses of 10 per cent solution. A few injections of 2 c.c. of 10 per cent salyrgan and 5 per cent theophylline were recently given and good results recorded. The diuretic results in a series of 100 mercurin suppository administrations were studied. Salyrgan suppositories were not tried in sufficient number for complete study but seem to be more irritating than mercurin. The order of the drug administration was varied so that the same drug was not always used first after the preparatory rest period. Sometimes the preliminary administration and the simultaneous administration of acid salts were carried out; other times these were omitted; while in 25 of the 100 mercurin suppository tests a preparatory enema was omitted.

TABLE I

Summary of Clinical Diuretic Effects

Number of Injections	Drug	Average Increase in Output of Urine			
		1st Day	2nd Day	3rd Day	Total in 3 Days
406	Mercupurin *	503%	180%	95%	778%
125	Mersalyl	341%	120%	62%	523%
29	Salyrgan and Theophylline	458.1%	193.4%	80.12%	732+%
70	Mercurin * Suppositories With Enema	264%	66%	25%	355%
25	Mercurin * Suppositories Without Enema	92%	41%	95%	228%

Recent data compiled by R. Swearingen.
* Supplied by Campbell Products, Inc., 79 Madison Avenue, New York, N. Y.

The summarized results in our diuretic studies are tabulated and the percentage of increases in the urinary output during the first, second and third 24 hour periods following the administration were computed. The output for the preceding or control day was used as the baseline for comparison. The control output of the control day was established in fairly fixed amounts by the conditions of the experiment, namely, the five day rest period preceding the administration. Calculations were done for me by Dr. C. C. Pearson, Dr. R. C. Douglass, Scott Martin, and Revace Swearingen, senior medical students employed under the N. Y. A. fund.

CLINICAL SUMMARY OF DIURETIC EFFECTS

A survey of all the data, taking into account the fact that the conditions were varied, now in favor of one drug and now in favor of the other, seems to show an advantage in favor of the combination preparation. Mercupurin seems to be the most efficient diuretic and at the same time the safest in as much as we have had no evidences of unfavorable reaction in over 400 intravenous injections. The new salyrgan-theophylline promises to be

a similarly most effective anti-edemic preparation. Mercury suppositories produced a diuresis in almost half of the cases during the first 24 hours after treatment; occasionally there was an increase for the three days following their use. A definitely better effect was obtained when an enema was used to prepare the bowel. Preliminary or concomitant administration of an acid salt likewise distinctly augmented the diuresis which resulted from mercurin suppositories as well as that from intravenous mercurials or combinations. Our results with the suppositories, however, have not been as spectacular as those reported by other investigators. In one instance we have noted renal irritation following the use of the newer preparation and in this case it appeared in a patient who had been previously given the intravenous mercurial without complications. Proctitis of a rather severe type was occasionally noted.

Comments

The results of the studies of the combination of mercurials and xanthines bear out the prediction of our earlier studies in which we pointed out the

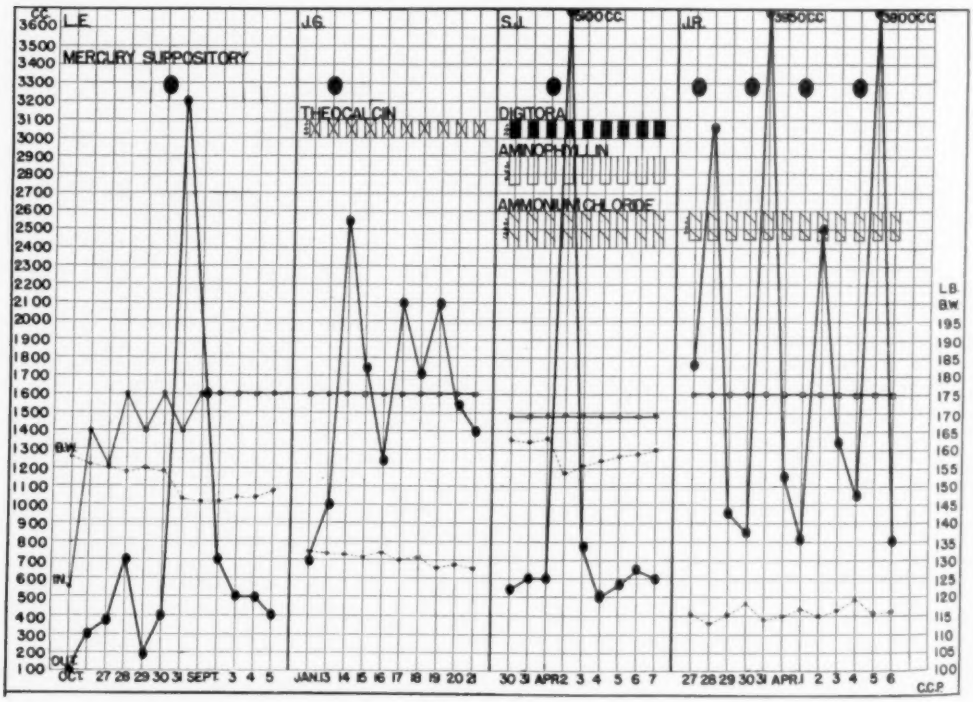

Fig. 8. Partial diuresis charts of four patients in whom mercurin suppositories were used.

augmentary effect of theophylline in combination with mercurials. Our clinical findings further confirm these contentions and those of some investigators in that the combination preparations of xanthines and mercurials

have advantages in the matter of diuretic efficiency as well as in safety over the pure mercurials.

The development of a mercurin suppository is a worthwhile forward step, even though they are effective in perhaps only 40 per cent of the cases and occasionally cause an albuminuria. It will be remembered that theophylline may be given by mouth in such instances and a combination effect may be secured. The acidosis producing salts, ammonium chloride or nitrate, are as a rule well tolerated but in nephritics with nitrogen retention they should not be used. Ammonium nitrate is better tolerated and hence preferable in cases in which renal function is borderline.

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INTERPRETATION OF THE ELECTROCARDIOGRAPHIC FINDINGS IN CALCAREOUS STENOSIS OF THE AORTIC VALVE *

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In the last few years distinct progress has been made in the clinical recognition of calcareous stenosis of the aortic valve. This is clearly exemplified by the fact that, as late as 1931, the lesion was only occasionally identified during the life of the patient whereas, today, its recognition is virtually a routine procedure. This high degree of diagnostic proficiency is chiefly the result of a determined and sustained effort to correlate the clinical signs with the postmortem findings. This has made the clinician alert, guiding him to utilize a special fluoroscopic technic [4, 6, 8, 9, 10] which in a remarkably high percentage of cases permits the demonstration of calcium in the valve leaflets, annulus, or both.

A clearer understanding of this lesion [2, 3, 5] has stimulated renewed interest in its various manifestations and necessitates a revision of current impressions regarding its incidence and the forms which it may assume. In a recent publication by Clawson and his coworkers, dealing exclusively with representative postmortem material, they were able to demonstrate calcium by gross methods of examination in 84 per cent of all cases of nonsyphilitic deformities of the aortic valve. In our recent survey of postmortem material at The Mayo Clinic [5] we found no instance of aortic stenosis without some deposit of calcium. Further to illustrate the fact that calcareous aortic stenosis is not a rare finding we cite this recent study [5] which revealed that this lesion occurs in 18.1 per cent of all cases of healed valvular defects encountered in routine postmortem examinations.

It therefore seems appropriate to call attention to additional diagnostic methods as they apply to the identification of this interesting valvular deformity. We refer to the occurrence and interpretation of electrocardiographic abnormalities.

Material

This study is based on 176 cases of calcareous aortic stenosis in which the electrocardiographic records were available. In 63 cases (35.8 per cent) the diagnosis was confirmed at necropsy and in 113 cases (64.2 per cent), the identification of the lesion was determined by clinical means together with fluoroscopic demonstration of calcification of the aortic leaflets or annulus.

In the postmortem material the degree of stenosis was distributed in the following manner: it was of grade 4 in 12 cases, of grade 3 in 28, of

* Received for publication April 23, 1938.

grade 2 in 20, and of grade 1 in three. It was shown in our previous study [5] that the degree of calcification closely paralleled the degree of stenosis. In 85 of the cases in which postmortem examination was not conducted, the diagnosis of calcareous aortic stenosis was made on the basis of the presence of classical physical signs and the clear-cut demonstration of calcification of the aortic valve by fluoroscopic means. In the remaining 28 cases in this group we concluded that the degree of stenosis was slight owing to the fact that all the classical physical signs were not present although calcification was demonstrable by fluoroscopy. These cases presented findings comparable with those of stenosis of grade 1 occurring in our postmortem material.

Factors Influencing the Electrocardiogram

The effect of a stenotic aortic orifice on the heart is obvious. The tremendous load imposed on the left ventricle becomes evident when one visualizes the extremely small opening that so frequently offers the only route for blood to gain entrance to the aorta. Increased work obviously eventuates in hypertrophy, and the most marked examples of cardiac hypertrophy are found in cases of marked calcareous stenosis of the aortic valve. In two cases in our series the heart weighed more than 1000 gm.

In cases in which aortic stenosis occurs as a solitary lesion, there being no additional factors to impose a further load on the heart, the stress is principally borne by the left ventricle. When aortic insufficiency occurs, hypertrophy of all the cardiac chambers may ensue, as shown by the studies of Levine and Carr. In our material the stenotic lesion was complicated by aortic insufficiency in 34.6 per cent of the cases. When mitral stenosis and other lesions exerting strain on the right ventricle coexist, this chamber hypertrophies and both sides of the heart participate in varying degrees in sharing the abnormal strain.

These facts are emphasized because a knowledge of physiologic principles is necessary to an interpretation of the electrocardiographic findings. On critical analysis of the electrocardiograms and careful correlation of the data obtained with the postmortem findings, it became evident that the established physical laws of electrocardiographic behavior [1] prevailed in this study. In the case of a lesion that predominantly imposes strain on the left ventricle it may be anticipated that the prevailing electrocardiographic configuration will reflect this strain, as evidenced by records displaying left axis deviation and T-wave negativity in Lead I or in Leads I and II. Exceptions to this are usually explained by antagonistic strain, myocardial injury, such as acute or healed infarcts, and the effect of digitalis, especially when administered in large quantities over a considerable period of time.

Analysis of Postmortem Material

Postmortem examination was conducted in 63 of the 176 cases of calcareous aortic stenosis (35.8 per cent) and these cases will be considered first and the data derived will then be applied to the clinical cases (table 1).

No Evidence of Ventricular Strain. Only six of the 63 cases (9.5 per cent) showed no electrocardiographic evidence of preponderant ventricular strain. In three cases, however, antagonistic right ventricular strain was coexistent, and this apparently neutralized the effect of the stenotic aortic

TABLE I

Evidence of Predominant Ventricular Strain *
Electrocardiographic Summary

Material	Cases	Per cent	No Ventricular Strain	Left Ventricular Strain	Right Ventricular Strain	T-wave Negativity in Leads I, II and III
Postmortem cases †	63	35.8	6	37	10	10
Clinical cases (marked stenosis)	85	48.3	12	50	7	16
Clinical cases (slight stenosis)	28	15.9	6	18	3	1
Total number	176		24	105	20	27
Per cent		100	13.6	59.7	11.4	15.3

* Associated valvular deformities and other lesions occurring in these groups are detailed in the text.

† All degrees of stenosis occur in this group.

orifice. There were three cases of well-marked mitral stenosis and in one case there was an associated mitral stenosis and aortic insufficiency. Auricular fibrillation was present in two cases.

Evidence of Left Ventricular Strain. Electrocardiographic evidence of left ventricular strain included left axis deviation and T-wave negativity (also diphasic T-waves) in Lead I or Leads I and II. Thirty-seven cases (58.7 per cent) presented these findings. In 20 cases T-wave negativity occurred in electrocardiograms with left axis deviation, in 14 cases left axis deviation was unassociated with T-wave negativity, and in three cases T-wave negativity occurred without axis deviation.

In seven cases mitral stenosis was also present; it was of grade 2 in five cases and of grade 3 in two cases. In eight cases there was an associated aortic insufficiency, in one of them in conjunction with mitral stenosis. In one case presenting left axis deviation, T-wave negativity in Leads I and II and auricular fibrillation, the calcareous deposit at the aortic valve extended into the aorta, almost completely obliterating the ostium of the left coronary artery and also reducing the size of the ostium of the right coronary artery.

When cases displaying evidence of left ventricular strain were analyzed according to the degrees of aortic stenosis, it was found that in two-thirds of them (64.8 per cent) the stenotic process was marked (grade 4 and 3), whereas in the remaining third (35.2 per cent), lesser degrees of stenosis were present (grades 2 and 1).

The weight of the heart ranged from 265 to 1170 gm., the average weight being 593.6 gm. Some interesting facts were gleaned on further analysis of these data, illustrating the fact that the presence of T-wave negativity in the electrocardiogram is proof of greater ventricular strain than axis deviation alone. When left axis deviation was the only graphic evidence of left ventricular strain the weight of the heart ranged from 265 to 875 gm., the average weight being 505.1 gm.; when in addition T-wave negativity in Lead I or in Leads I and II was present, the weight of the heart was considerably greater. The lowest weight was 356 gm. and the highest was 1170 gm.; the average weight was 650.5 gm., or an average of 145.4 gm. greater than in cases displaying only left axis deviation.

There were only five cases (13.5 per cent) of auricular fibrillation in this group and in no instance was mitral stenosis an associated finding.

Evidence of Right Ventricular Strain. In this group of cases the electrocardiograms exhibited either right or left axis deviation and T-wave negativity (also diphasic T-waves) in Leads II and III. There were 10 such cases (15.9 per cent); all but two showed T-wave negativity and these displayed right axis deviation and auricular fibrillation. Six cases showed right axis deviation, three left axis deviation, and the remaining one showed no axis deviation but T-wave negativity in Leads II and III.

Cases presenting evidence of predominant right ventricular strain in the presence of a mechanical barrier that outstandingly imposes its burden on the left ventricle are obviously of unusual interest as at first glance they appear to be exceptions to the recognized laws of electrocardiography. When these cases received critical analysis and when the additional findings were carefully appraised, however, it was found that only two remained exceptions to the general rule. Five cases showed well-marked mitral stenosis (grades 3, 3, 3, 2, 2); in three of them there was an associated aortic insufficiency and, in one case, digitalis had been administered beyond the point of tolerance. The sixth patient presented an advanced degree of pulmonary arteriolar atherosclerosis, a disease notorious for its imposition of work on the right ventricle. The seventh and eighth patients both had infarction of the posterior basal portion of the left ventricle which characteristically results in T-wave negativity in Leads II and III. The infarcts in both cases were old but their presence remained as electrocardiographic relics.

In analyzing these cases in which the electrocardiograms displayed predominant strain of the right ventricle with reference to the degree of aortic stenosis it was found that, in five, the stenotic process was marked (grades 4 and 3), in five there were lesser degrees of stenosis (grade 2). However, in two cases in which the degree of aortic stenosis was marked, healed infarcts involved the posterior basal surface of the left ventricle.

The weight of the heart in this group ranged from 360 to 862 gm., the average weight being 629.3 gm., or a value slightly greater than the average weight of the heart for cases showing evidence of predominant strain of the left ventricle (593.6 gm.).

Auricular fibrillation occurred in three cases (30 per cent), which was a relatively higher incidence than in cases showing predominant left ventricular strain (13.5 per cent). In two cases mitral stenosis and aortic insufficiency were associated findings.

Cases Presenting T-wave Negativity in Leads I, II, and III. These cases are of unusual interest and combine certain features of the two preceding groups. There were 10 cases (15.9 per cent) in this group. There were no instances of right axis deviation; four cases showed left axis deviation, and in the remaining six cases no axis deviation occurred. Only one case with mitral stenosis was recorded (grade 3). Aortic insufficiency was present in half the cases, and in one of them the pericardial cavity was almost obliterated by old adhesions. In another case the deposit of calcium at the aortic valve extended downward to invade the aortic cusp of the mitral valve and upward into the aorta, partially occluding the ostium of the left coronary artery. Thus there were only three cases in this group in which no lesions except the aortic stenosis were demonstrable. Marked degrees of aortic stenosis (grades 4 and 3) were present in all cases except one (grade 2).

The weight of the heart ranged from 434 to 892 gm., the average weight being 581.6 gm. This average weight was quite comparable to that for cases showing evidence of predominant left ventricular strain (593.6 gm.).

Auricular fibrillation occurred in only one case.

Disturbances in Cardiac Conduction. Defects in cardiac conduction were recorded in only eight cases (12.7 per cent). There was one case with complete heart block in which the nodular excrescence of calcium extended from the mitral cusp of the aortic valve in such a manner as to involve the bundle of His. There were four instances of incomplete bundle-branch block and three cases showed evidence of delayed auriculoventricular conduction.

Comment. Only eight of the 63 cases in this group proved on analysis to be exceptions to the general laws of electrocardiographic behavior. In three cases there was no evidence of predominant ventricular strain, in two cases there was predominant right ventricular strain, and in three cases there was T-wave negativity in Leads I, II and III. In spite of these exceptions, however, the correlations for the group were remarkably accurate.

Analysis of Clinical Cases Showing Marked Calcareous Stenosis

There were 85 cases (48.3 per cent of the total of 176) in which the clinical findings unequivocally demanded the diagnosis of calcareous stenosis of the aortic valve and in which fluoroscopic examination clearly demonstrated calcification of the aortic leaflets or annulus. When the clinical findings in this group were compared to those in the postmortem group they were found to agree closely in respect to the more marked grades of stenosis,

permitting the presumption that this group of clinical cases represented well-advanced examples of calcareous aortic stenosis.

No Evidence of Ventricular Strain. In 12 (14.1 per cent) of the cases there was no graphic evidence of preponderant ventricular strain, that is, axis deviation and T-wave negativity. There were no instances of mitral stenosis, but aortic insufficiency was present in seven cases. Auricular fibrillation was recorded in one case.

Evidence of Left Ventricular Strain. It is interesting to note how closely the data for this group of cases agree with those for the postmortem group. Fifty cases (58.8 per cent) revealed electrocardiographic evidence of predominant strain on the left ventricle. In 25 cases T-wave negativity in Lead I or in Leads I and II occurred in electrocardiograms showing left axis deviation; in 19 cases left axis deviation was unassociated with T-wave negativity and in six cases T-wave negativity occurred without left axis deviation.

Mitral stenosis was identified in only two cases. The recognition of mitral stenosis in the presence of well-marked stenosis of the aortic valve is often difficult owing to the fact that the extremely loud and rough systolic murmur of the aortic lesion with its widespread propagation may obliterate the less conspicuous signs of mitral stenosis. This undoubtedly accounts for the extremely low incidence of mitral stenosis in this group. Aortic insufficiency occurred in 21 cases. Auricular fibrillation was recorded in nine cases (18 per cent), and was associated with aortic insufficiency in five cases.

Evidence of Right Ventricular Strain. Seven cases (8.2 per cent) comprised this group. In two cases the electrocardiograms revealed right axis deviation in addition to T-wave negativity in Leads II and III. It is significant to note that mitral stenosis was diagnosed in six cases. The fact that mitral stenosis was identified in such a high percentage of cases in this group suggests the probability that the lesion was well marked and therefore its clinical expressions were not obscured by those of the stenotic aortic valve. It is also possible that the degree of mitral stenosis exceeded that of the aortic valve. Four cases also showed aortic insufficiency, in each case coexistent with mitral stenosis.

Auricular fibrillation occurred in three cases (42.9 per cent) of this group, in each instance in cases with mitral stenosis and aortic insufficiency.

Cases Presenting T-Wave Negativity in Leads I, II and III. There were 16 cases (18.9 per cent) showing this electrocardiographic configuration. Left axis deviation occurred in four cases, right axis deviation in two, and there was no axis deviation in 10 cases. Mitral stenosis was identified in only one case, while aortic insufficiency occurred in eight cases. One patient had received digitalis beyond the limit of tolerance and this may have influenced the electrocardiogram.

No instance of auricular fibrillation was recorded in this group.

Disturbances in Cardiac Conduction. In two cases there was complete heart block, in six incomplete bundle-branch block, and in one case there was complete left bundle-branch block. In five other cases delayed auriculo-ventricular conduction was demonstrated.

Analysis of Clinical Cases Showing Only Slight Calcareous Stenosis

In this group of 28 cases all the clinical signs of calcareous stenosis of the aortic valve were not present but fluoroscopic examination revealed the presence of calcium in the valve leaflets or annulus. The clinical findings in this group closely corresponded with those for grade 1 stenosis in the post-mortem material and are assumed to represent similar cases.

No Evidence of Ventricular Strain. There were six cases (21.4 per cent) without axis deviation or T-wave negativity. No associated valvular lesions were demonstrated and there was no instance of auricular fibrillation.

Evidence of Left Ventricular Strain. There were 18 cases (64.3 per cent) presenting electrocardiographic evidences of predominant strain on the left ventricle. In five cases T-wave negativity in Lead I or Leads I and II occurred in records showing left axis deviation, in 11 cases left axis deviation occurred without T-wave negativity and in two cases, T-wave negativity occurred without axis deviation.

There was no instance of mitral stenosis in this group but, in three cases, aortic insufficiency occurred. Auricular fibrillation was present in only one case.

Evidence of Right Ventricular Strain. These findings occurred in three cases (10.7 per cent). T-wave negativity in Leads II and III was recorded in two cases, one of which showed left axis deviation. In the third case the electrocardiogram showed right axis deviation. There was no instance of mitral stenosis, but there was one case with aortic insufficiency. Auricular fibrillation was not observed.

Cases Presenting T-wave Negativity in Leads I, II and III. There was only one case (3.6 per cent) in this group. No associated valvular defects were noted.

Disturbances in Cardio-Conduction. None were observed in the cases in this group.

Summary

The electrocardiographic findings in 176 cases of calcareous stenosis of the aortic valve are presented. The records were analyzed with special reference to graphic configurations conforming to the generally accepted laws of predominant ventricular strain. A very high correlation between electrocardiographic variations and pathologic lesions was disclosed for the postmortem material, only eight cases proving to be exceptions to the rule.

In clinical cases the same opportunity for comparable correlations was

obviously not afforded, although a similar tendency toward correlation was disclosed when the data on the postmortem cases were applied to them.

Auricular fibrillation occurred infrequently, only 25 instances (14.2 per cent) being recorded for the entire series. In six cases auricular fibrillation occurred in the presence of mitral stenosis and aortic insufficiency, and in seven other cases in the presence of aortic insufficiency alone.

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ASTHMATOID HEART FAILURE; A FORM OF LEFT VENTRICULAR FAILURE AND ITS DIFFERENTIATION FROM BRONCHIAL ASTHMA BY CIRCULATION TIME AND OTHER CRITERIA *

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The diagnosis of bronchial asthma on an allergic basis when symptoms appear for the first time late in life should be made with great caution. Only 12 to 18 per cent of all cases have their onset in the fifth and sixth decades and less than 2 per cent after the age of sixty.[1] It is during this period of life that many of the conditions which must be considered in the differential diagnosis of bronchial asthma first make their appearance and all of these should be ruled out before the presumptive diagnosis of allergic asthma can be made.

Prominent among the diseases presenting difficulties in diagnosis is heart failure. It is the purpose of this paper to reëmphasize this important point in differential diagnosis, to reiterate the criteria of differentiation and to point out that some forms of left ventricular failure produce a paroxysmal dyspnea indistinguishable by symptoms, physical signs or therapeutic response from bronchial asthma.

In an excellent clinical and pathological consideration of fatal "asthma," Lamson and Butt [2] have shown how often patients with true allergic asthma have and succumb to cardiac disease and how often the wheezing of patients diagnosed as having asthma is shown at autopsy to be the result of renal, cardiac, bronchial or neoplastic disease. They cite insurance statistics [3] to show how much higher the death rate is among asthmatics as compared with the expected average. Much of this excess occurs in deaths which are the results of organic heart disease and Dublin and Marks [4] have shown that in male asthmatics the heart disease mortality is two and one-third times the normal. It is not quite clear from their statistics whether the diagnoses of bronchial asthma were erroneous or whether the incidence of heart disease was greater among allergic asthmatics. Both factors are probably operative, but in any case it should be quite clear that the belief of many clinicians that bronchial asthma carries with it an excellent life expectancy and may be treated as an essentially harmless disease should be revised.

As has been pointed out before, the term bronchial asthma is used in this paper in the restricted sense of allergic asthma but is often used more loosely. Bronchial asthma has been defined as [17] "a form of paroxysmal dyspnea, the characteristic feature of which is a marked diminution or arrest of the respiratory movement with prolonged expiration." If this definition is

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accepted and if cognizance is taken of the origin of the word (from the Greek " hard breathing ") then it is justifiable to apply the term asthma to any condition which satisfies the definition of Norris and Landis. Certainly the use of " cardiac asthma " to cover the several forms of paroxysmal dyspnea in heart disease is etymologically correct and convenient.[5]

In this paper the terms cardiac asthma and left ventricular failure will be applied only to those forms of failure in which wheezing respirations are the dominant feature. Other types of left ventricular failure, while clinically important, have been disregarded in this study. Those cases in which there was wheezing respiration without basal or moist râles so that the physical signs resembled closely those of bronchial asthma have been called " asthmatoid " heart failure.

Pathogenesis of the Paroxysm of Cardiac Asthma

During an attack of cardiac asthma the patient will be found to present two sets of pulmonary signs: the first, those present before the attack, such as basal râles, signs of effusion, pneumonitis, atelectasis, infarction, emphysema, etc., and the second, an accentuation of these signs or, more often, new, temporary signs, conspicuously, wheezing respiration, prolonged expiration, basal râles not previously present and signs of pulmonary edema. Most often the second group is dependent, according to modern concepts of the pathogenesis, on left ventricular weakness and on pressure differences between the right and left sides of the heart leading to sudden damming of blood in the pulmonary circuit. There are some cases, such as those attacks of paroxysmal dyspnea occurring as an initial symptom in cerebral embolism or embolism elsewhere, which may be dependent on reflex nervous influences acting through or independent of changes in the pulmonary circulation. In any event, disregarding basal or bubbling râles which cannot be confused as a rule with bronchial asthma, the signs are dependent on the same factors as those concerned in allergic asthma; namely, narrowing of the lumina of the smaller bronchioles either by direct muscular spasm or by swelling of the bronchiolar mucosae or by edema fluid or other detritus obstructing the lumen. Temporary emphysema may also play a rôle. These changes usually differ in degree and in quality from those observed in allergic asthma so that, although asthmatoid breathing is often a conspicuous feature, there is seldom any question of differential diagnosis. Occasionally, as we shall see, asthmatoid respirations and wheezes may dominate the picture so completely that accurate diagnosis is often impossible during the attack.

Bronchial spasm may actually occur, according to MacKenzie,[6] as a reflex disturbance produced by the weakened heart. I believe that if reflex bronchial spasm occurs, it may follow changes other than sudden cardiac weakness, such as cerebral embolism. As Pratt points out, peripheral factors must be considered in view of the hypertension, profuse sweating and

cold skin which are often found indicating peripheral vasomotor changes and an associated "medical shock" may be present. Eppinger and others [7] showed that in some cases the blood flow from the arteries to the veins is increased during cardiac asthma.

Excellent accounts of the pathological changes in the lungs have been published so that here the discussion will be confined to those changes which may produce wheezing respiration.[8] Microscopically the air space is diminished by an intense engorgement of the capillaries which may protrude far into the alveoli which contain erythrocytes, leukocytes, desquamated alveolar epithelia and large mononuclear cells containing hemosiderin, the heart failure cells. Hyperplasia of the collagenous framework and of the reticulum, elastic and muscle fibers may occur. Corpora amylacea are not uncommon. When pulmonary edema supervenes, the alveoli, bronchioles, bronchi and trachea may be filled by frothy fluid. "Pulmonary edema differs from edema in other parts of the body in that the fluid is not almost entirely in the interstices of the tissue, but much more in the alveolar lumens, which are really outside of the physiological interior of the body. The reason for this peculiarity seems to be in the morphological adaptation of the lung to its respiratory function. The capillaries lie very close to the surface of the alveoli and are covered by only a thin layer of alveolar epithelium, which probably does not form a continuous covering. The result is that fluid which transudes from the capillaries immediately finds its way into the alveolar spaces. Because the fluid is rich in protein, it coagulates during the preparation of the sections, and is seen in hematoxylin-eosin preparations as pink-stained substance filling out the affected alveoli. Within it are vacuoles due to air bubbles. The fluid contains varying numbers of blood and alveolar cells, but in non-inflammatory edema these are usually not numerous. When the alveoli are distended by the edema fluid, the interalveolar septa are compressed and the capillaries collapsed." [8]

During the attack there is usually emphysema, either temporary or an accentuation of a previously existing condition. The diaphragm is low, and the thorax is held in the position of full inspiration. Clinically, there is hyperresonance, increased antero-posterior diameter of the chest, diminished breath sounds, partial or complete obliteration of the absolute cardiac dullness and diminished movements of the diaphragm. The increased thoracic volume is occupied partly by increased amounts of blood in the vascular bed of the lung, partly by transudation of edema fluid into the pericapillary and intra-alveolar space and probably by an increase in the total volume of free air space.[9]

Parker and Weiss [10] have distinguished between pericapillary edema and intra-alveolar edema and demonstrate that one may occur without the other. They feel that this may account for the lack of correlation between dyspnea, on the one hand, and clinical signs such as pulmonary râles, on the other hand, in certain cases of heart failure. They show that without edema fluid within the alveolar space there may be edema in the alveolar wall and

interlobular septa with increased amounts of collagen and thickening of the alveoli. These may contribute to the "Lungenstarre" (stiffening of the lungs) described by von Basch.[11] It is an interesting hypothesis that some similar change may be found in the type of case described here. We plan to examine the smaller bronchioles of patients who may die in asthmatoid heart failure without basal râles to determine if their walls contain edema without free fluid within the lumina. It is possible of course, as in the case of allergic asthma, for exudate in the bronchioles to produce wheezing râles by narrowing the air passages. This is undoubtedly the mechanism in those patients showing basal râles as well.

Three cases have been selected from among our case histories to illustrate several phases of the problem. Each case has a brief comment, and a consideration of differential diagnosis will follow in a separate section.

Case Reports

1. *Left Ventricular Failure Simulating Allergic Asthma.* M. M., a married Italian woman of 33, was admitted to the service of Dr. Tasker Howard in a paroxysm of dyspnea with the diagnosis of bronchial asthma. For several months there had been intermittent difficulty in breathing and the subjective sensation of "wheezing." There was no past or familial history of allergic disease. The lungs, according to the note of the admitting physician, showed "typical signs of bronchial asthma," sibilant and sonorous wheezes scattered evenly throughout both lungs, anteriorly and posteriorly. There were no moist or basal râles. Expiration was prolonged throughout. There were no clinical signs of right heart failure such as hepatic enlargement or peripheral edema but the presence of mitral stenosis led to further investigation of the cardiac status. On close questioning, the patient admitted the presence of increasing orthopnea and of dyspnea on exertion during the period covered by her chief complaint. The wheezing was worse at night and with the patient recumbent. Further examination revealed a venous pressure of 15 cm. of water and indirect evidence of increased pressure in the pulmonary circulation: accentuation of the pulmonary second sound, increase in the size of the pulmonary conus and roentgen-ray evidence of passive congestion in the lungs. The electrocardiogram showed right axis deviation. The circulation time (cyanide method) was 34 seconds; the ether time (arm-to-lung method of Hitzig) was 10 seconds; the "left heart" time (by subtraction) was 24 seconds or markedly prolonged. Adrenalin gave moderate transient relief but improvement was striking only after treatment directed toward correction of the cardiac failure, digitalization, sedatives, rest and fluid restriction. The patient was discharged 10 days later much improved and with no asthmatoid signs in the chest.

Comment. A case closely simulating allergic asthma even with respect to relief with adrenalin. It is somewhat unusual in that the asthmatoid dyspnea followed mitral stenosis. Most cases of this type occur in the course of hypertensive heart disease. It should be noted of course that the administration of adrenalin to a patient in cardiac failure may not be without considerable danger.

2. *Allergic Asthma with Incidental Heart Disease.* Y. B., married white Jewess of 59, was admitted to the service of Dr. Tasker Howard during a paroxysm of dyspnea, the lungs showing signs identical with those of case 1. There was a

complaint of wheezing respirations and "choking spells" occurring especially at night for the past year. The past history was completely negative for allergy but a brother and two children have hay fever. The temperature on admission was 101.4° and the leukocyte count was 17,400 with 7 per cent eosinophiles. The blood pressure was 140 mm. of mercury systolic and 80 diastolic, the pulse 120 and regular. The heart was not enlarged and showed no murmurs. The venous pressure during the paroxysm was 22 cm. of water, subsiding thereafter to the normal level of 7.8. The circulation time was 15.0 seconds and the ether time 7.0 seconds, both normal. There was striking relief with adrenalin but before admission the patient had been told that she had cardiac asthma and was advised against the use of adrenalin. The electrocardiogram showed a right bundle branch block.

Comment. The diagnosis here was not easy during the paroxysm. Abrupt onset of allergic asthma is very unusual at the age of 58 and the increased venous pressure and electrocardiographic changes suggested heart disease. However, the positive family history, the eosinophilia, the lack of any evidence of congestive failure, the lowering of the venous pressure after the paroxysm, the precipitation of the attacks by bouts of febrile bronchitis, the normal circulation time all establish the diagnosis of bronchial asthma. The patient was treated on this basis and was discharged relieved.

Allergic asthma appearing late in life may simulate heart disease. Electrocardiographic findings indicated myocardial damage which had no relationship to the attack. Prompt response to adrenalin is somewhat in favor of allergic disease but not conclusive. Note that the paroxysms occurred especially at night as in case 1 and that the venous pressure was elevated when first taken.

3. *Left Ventricular Failure in a Patient with Allergic Asthma.* H. V., a married American man of 55, was admitted to the service of Dr. Carl H. Greene during a bout of dyspnea. The physical findings in the lungs were identical with those found in the first two cases. The patient had a long standing glomerulonephritis and hypertension and signs of both right and left heart failure without, however, basal râles. The cyanide and pulmonary circulation times were both prolonged, 31 and 17 seconds respectively. The patient responded promptly to morphine, digitalis, and venesection. There was an eosinophilia of 9 per cent and some persistence of sibilant râles after the cardiac failure was improved. It was then discovered that the patient was a furrier with long standing allergic asthma for which he had been treated and for which he had positive skin tests.

Comment. As in this case, a patient with allergic asthma may develop left ventricular failure.[18] When in doubt, it is better to treat both conditions. Increased pulmonary pressure may increase the asthmatoid signs and symptoms of allergic asthma. Finding all the criteria of true bronchial asthma should not rule out heart failure.

Differential Diagnosis

Blood Count. Eosinophilia is a clue to the diagnosis of bronchial asthma but it may occur in other diseases or in a complicating heart failure. Polycythemia is often present secondary to the pulmonary changes of either disease and is not diagnostic.

Roentgen-Ray Diagnosis. Roentgenography, while useful, is rarely conclusive. Infarcts, bronchopneumonia patches, pleural effusions, effusions into the interlobar spaces are often found but these cases rarely present difficulties in differential diagnosis. The hilar shadows are usually enlarged, sometimes to a very marked degree. There is sometimes a fanlike radiation toward the periphery and particularly toward the base of the lung. Pezzi [12] has termed the expansile pulsation of the hilar shadows occasionally seen in left heart failure the "hilar dance." All increases in hilar shadow usually decrease with response to therapy. The lung markings are increased in left heart failure and are sometimes difficult to distinguish from bronchopneumonia. The lung fields in cases of pulmonary engorgement appear denser than usual. Fluoroscopically, markedly diminished excursion of the left ventricle contrasting vividly with good excursion of the right cardiac border may be seen in the left oblique position.[9]

Examination of the Heart. This need not be discussed in detail. The findings are those of the underlying heart disease, usually hypertensive heart disease although occasionally rheumatic endocarditis as in our first case. The pulmonic second sound may be sharply accentuated because of the increased tension in the pulmonary circulation. The heart sounds may be poor but are sometimes surprisingly good. The accompanying emphysema, whether temporary or permanent, usually precludes accurate percussion. Palpation of the apical impulse may help in determining the size of the heart.

Physical Signs in the Lungs. If basal râles or signs of effusion are present, the diagnosis of cardiac asthma may be fairly easy. In the group of cases under discussion, a small percentage of the total number of cases of left ventricular failure, the signs may be indistinguishable from those of allergic asthma with accompanying emphysema. The diaphragm is low, expiration is prolonged, the chest is held in an inspiratory position, the percussion note is hyperresonant, there is no post-expiratory pause and scattered throughout both lungs, front and back, are sibilant and sonorous râles and rhonchi. Note should be made here of the occasional case of left ventricular failure without râles of any sort in whom the only lung signs are those of rapid respiration, usually with cyanosis and transient emphysema.

History and Response to Adrenalin. A positive history for allergic conditions in the patient or his family or of a satisfactory response to adrenalin is not, as we have seen, adequate evidence that the attack is not cardiac in origin. Onset in late life and nocturnal incidence of dyspnea favor heart failure but are not conclusive as was shown in case 2.

Venous Pressure Determinations. These have been proposed to distinguish between cardiac and bronchial dyspnea. It is true that if the patient can be put under basal conditions, the venous pressure is usually normal in bronchial asthma in contrast to the elevation in right heart failure. There are two drawbacks to the use of this method, first, that there are occasional cases of isolated left heart failure in which the venous pressure may not be elevated and second, that during an acute paroxysm which is the time

when differential diagnosis is most difficult the venous pressure of the asthmatic is usually sharply elevated no matter what the cause. We have not felt that the venous pressure is of much value in diagnosis during an acute paroxysm.

Circulation Times. Measurement of the circulation time was found to be the most satisfactory method of differential diagnosis. During left ventricular failure, the velocity of blood flow through the pulmonary circuit is markedly decreased so that total circulation times are increased. Usually there is an associated slowing of the stream in the systemic circuit as well, so that the arm-to-lung times are increased thus prolonging still more the total time. In unusual cases, there may be isolated left heart decompensation so that the arm-to-lung time is normal and the total time increased. Following the lead of Oppenheimer and Hitzig,[13] we have found that measurement of blood velocity has been exceedingly useful in the diagnosis of cardiac asthma and we have been able at the Kings County Hospital to confirm their results. Our methods differed slightly in that we used sodium cyanide [14] for measurement of the total circulation time in place of saccharin. Calcium gluconate and saccharin were used in a few cases but we have felt that the cyanide method gives a sharp end-point, does not depend on a subjective reaction and is more satisfactory in the acutely ill patient. The figures obtained with any of the three measures check closely with one another. For the arm-to-lung time we have used the ether method of Hitzig [15] which we have found fully satisfactory. 0.3 c.c. of ether and an equal amount of physiological saline were injected rapidly into an arm vein and the length of time elapsing until the ether vapor is perceived in the patient's breath was measured. The "left heart" time is obtained by deducting the ether time from the cyanide time.

The total circulation time in 37 cases of bronchial asthma was found to be within normal limits or somewhat decreased. When measurements were taken during a severe paroxysm (the period during which it is necessary to differentiate heart failure) the rate in one-third of the cases was appreciably increased. This increase in blood velocity is undoubtedly due to the fact that the patient is straining during a paroxysm and is not under basal conditions. It will be seen, therefore, that the error introduced into the test by reason of the fact that the subject has not been resting and is not under basal conditions is in the direction of making the venous pressure less sensitive as a differential diagnostic point and of making the circulation time a more sensitive test in that it accentuates the differences in blood velocities in bronchial and cardiac asthma.

There were 49 cases of left ventricular failure observed during the time in which these tests were made. Forty showed basal râles and nine showed signs of asthmatoid failure, the type of case, namely, which is under primary discussion in this paper. All nine cases showed decreased blood velocity both total and pulmonary. Of the other 40 cases, in one a satisfactory end-point was not established, in three all three circulation measurements

were normal, and in 36 the total circulation time was prolonged. In all 36 the "left heart" time was prolonged and in 21 the arm-to-lung time was prolonged. There were, therefore, 15 cases of isolated left ventricular failure and, if to these the nine cases of asthmatoid failure are added, there are a total of 24 cases of left ventricular failure without demonstrable involvement of the right heart. These figures are shown in table 1.

TABLE I

Circulation Times in 49 Cases of Left Ventricular Failure with Wheezing Respiration as Dominant Physical Sign

		Total Time (cyanide)		Pulmonary Time*	
		Normal	Prolonged	Normal	Prolonged
Unsatisfactory endpoint	1				
Isolated left vent. failure	24				
Rt. plus left vent. failure	24				
"Asthmatoid failure" (Wheezing resp., no basal râles)	9	0	9	0	9
Left vent. failure with basal râles	40	3	36	3	36

* Obtained by subtraction of ether time from cyanide time. 24 cases of the total series showed normal ether times. This is referred to also as the "left heart" time. A more recent method of estimating this time is described by Gubner, et al.[19]

In 11 cases in which there was improvement in symptoms following digitalization, the circulation times were repeated where previous readings had indicated failure of the left ventricle alone. In nine of these cases there was a prompt improvement in the pulmonary blood velocity paralleling closely the clinical improvement although in only three did the circulation time return to normal or less by the time the patient was ready to get out of bed. In two other cases of the eleven there was also an improvement in the circulation time, but this lagged considerably behind the clinical improvement. These findings confirm our clinical opinion that failure of the left heart responds approximately to the same measures, digitalis, etc., to which right heart failure responds. No special effort was made to assess the value of venesection in improving the blood velocities. These findings, with respect to the effect of digitalis, and in general the other findings mentioned in this section of the paper confirm the findings of Hitzig, et al.[16] reported in their excellent study in 1935.

COMMENT

Wheezing respiration is commonly found in heart failure and may indeed be the only physical sign present in the lungs, occurring without the basal râles usually present in heart failure. In rare cases, rapid breathing may be the only physical sign in left heart failure. Wheezing decompensation, especially in the type in which there are no basal râles and designated

as "asthmatoid heart failure" in this paper, are sometimes distinguished only with great difficulty from bronchial asthma. This is especially true in those cases of bronchial asthma in which there are moist as well as wheezing râles or in which there may be some degree of right heart failure.

The pathogenesis of wheezing respiration in heart failure is discussed in the body of the paper and it is suggested that, as in allergic asthma, narrowing of the lumina of the smaller bronchi and bronchioles may be caused by spasm, exudate and edematous involvement of the walls in varying degrees.

Case histories illustrating certain aspects of the problem are given and other cases in the series are analyzed in two tables. The differential diagnosis is discussed in some detail and it is reëmphasized that by physical examination and response to adrenalin it may be impossible to distinguish between cardiac and allergic asthma during, or shortly after a paroxysm. Measurement of the venous pressure is not considered an adequate differential diagnostic point.

TABLE II

Classification of Cases According to Primary Diagnosis

	Isolated Left Failure		Combined Right and Left Failure
	Without Basal Râles	With Basal Râles	
Rheumatic endocarditis	3	2	11
Mitral stenosis	1	2	2
Aortic insufficiency	1		3
Aortic stenosis			1
Combined aortic and mitral	1		5
Syphilitic heart disease	1	1	2
Chronic glomerulo-nephritis	1	2	3
Hypertensive heart disease	3	9	6
Coronary disease	1	1	2

Following the work of Hitzig, King, Fishberg and Oppenheimer, it was found that circulation times enabled us to diagnose cardiac asthma rapidly. Arm-to-lung (ether), arm-to-carotid (cyanide), and pulmonary circuit times were utilized. In many cases, left ventricular failure was accompanied by some degree of right heart failure but in some cases there was isolated left-sided decompensation. In most cases digitalis increased the velocity of blood flow through the pulmonary circuit just as it increases the blood velocity in the systemic circuit in right heart decompensation.

CONCLUSIONS

1. Wheezing respiration is common in left ventricular failure. It may occur without basal râles ("asthmatoid heart failure") in which case it closely simulates allergic asthma in symptoms, physical signs and response to adrenalin.

2. The pathogenesis is discussed and illustrative cases given.

3. The quickest and easiest method of determining whether or not a case of paroxysmal dyspnea is cardiac in origin is by means of a study of the circulation times which show decreased blood velocity in the pulmonary circuit. Arm-to-carotid (cyanide) and arm-to-lung (ether) times may be quickly and accurately determined at the bedside. They are more reliable in the differential diagnosis than determinations of the venous pressure.

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SUGGESTED REVISIONS OF MEDICAL PHARMACOLOGY *

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THE recent cure of general bacterial infections with drugs of the sulfonamide group should bury forever the belief that treatment by drugs can be palliative only. It might seem, therefore, that this were as inopportune a time as could be chosen to speak of the failure of pharmacology and to consider reorganization. Science, however, does not progress entirely by revolutionary discoveries, and, although the cure of infections by drugs undoubtedly will stimulate interest in pharmacology for a time, the widespread dissatisfaction which exists will become evident again if there is any fundamental cause for it. It would, therefore, seem well to discover, if possible, why it is that Dr. William D. Cutter, Secretary of the American Medical Association Council on Medical Education and Hospitals, in a recent public address,[1] stated that pharmacology should be either discontinued or reorganized; why it was that the pharmacologists of this country, as well as of Europe, recently met to discuss their difficulties; why two of our newest and most highly endowed schools of medicine failed to provide separate departments of pharmacology; and why others have spent several years trying to decide whether to drop the subject, combine it with physiology or biochemistry, or replace it by a therapeutic institute with a clinician at its head. Well over one hundred articles on the status of pharmacology, materia medica, and therapeutics may be found in the literature,[2-55] among which those by Griesinger,[2] Küchenmeister,[3] Fraser,[4] Beyer,[5] Jerome,[7] Abel,[10] Hill,[12] Sollmann,[13] Cushny,[21] Edmunds,[27] Dixon,[28] Bierring,[30] Handovsky,[31] Meyer,[32] Jarisch,[33] Clark,[34] Edmunds,[38] Starkenstein,[40] Seel,[47] DeGraff,[49] Edmunds,[50] Hayman,[51] Heubner,[52] and MacNider [53] are of particular interest. No conclusions seem to have been reached other than that pharmacology has not received the proper support. The present situation is an anomalous one. Everyone wants to know more pharmacology, all admit that some of the best men are in this field and that their work is of the highest type, and yet dissatisfaction with this subject is very prevalent.

Several years ago a note was published by the present author,[56] suggesting a fundamental cause of our difficulties, which could be remedied by simple means. The cause was considered to be that pharmacologists are not studying the human organism as are all others in medicine, but they are, at least by definition, studying drugs and their actions. The difference between studying the reaction of the organism to drugs and the "action" of drugs on the organism may seem of little importance or nonexistent. It is,

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however, the object of this communication to show how fundamental this difference is; to urge that we give up once for all the study of drugs and their actions, which, in spite of anything to the contrary, is pharmacy, and develop a medical science, the object of which is the study of the human organism by means of its reaction to chemical substances, a systematic method for doing which is described. Before taking this up in detail, it might be well to consider briefly what we mean by pharmacology, as well as its relation to other branches of medicine.

Buchheim's Pharmacology

When magic was supposed to reside in drugs and cause the remarkable disturbances seen in man when these were taken by him, it was a scientific procedure to examine all manner of plants for such magical actions. Later it became equally, if not more, interesting to discover what this magic was which drugs contained. When, however, through such studies the science of chemistry was developed and it was found that the magic consisted of chemical molecules, the interest and science of the study of drugs were gone, and pharmacy, the father of all science perhaps, became an art, and plant and animal tissues no longer had any interest as such to the pharmacists but merely as sources of chemical substances which had, or might have, "actions" in man.

In the middle of the nineteenth century materia medica, the remnant of pharmacy left in our schools of medicine, was a chaos of fact and fancy. Schmiedeberg [57] gives a very graphic description of it: "What at that time under the name of materia medica existed as a medical discipline could hardly be spoken of as a science. Its contents consisted of a massive sum of experience and of minutely described directions and rules for the use of an infinite number of drugs and preparations, of which the action and use in sickness was based on intuition and assumptions which owed their origin to the dogma of natural philosophy."

The fearful task of separating from this confused mass of data that which had some probability of factuality and that which was purely speculative was undertaken by Rudolf Buchheim in Dorpat. Buchheim was a great scholar, not only in the languages, but in chemistry, physiology, pharmacy, botany, and medicine. He was editor-in-chief of the *Pharmaceutischen Centralblattes,* which later became the *Chemisches Centralblatt.* He also supplied the reports of physiological chemistry in Schmidt's *Jahrbüchern der Medicin.* He was an active investigator. Four years spent in translating and reorganizing the 1,700 pages of Pereira's "Handbuch der Arzneimittellehre" showed him the need for a different way of dealing with drugs in medicine.

Although individuals in France, England, and Germany had experimented with drugs on animals, it was Buchheim who recognized the necessity for a systematic attack on the problem in order to discover how drugs act. In his own house, with his own money, Buchheim established the first

pharmacological laboratory for the experimental study of the action of drugs. This laboratory was later taken over by the University of Dorpat and Buchheim's title changed from that of Professor of Arzneimittellehre, Diätetik und Geschichte und Encyklopädie der Medicin, to Professor of Pharmacology. Pharmacology from φάρμακον, a drug, and λογια, speak, was defined as the study of drugs and their actions. Pharmacology is, however, an old word used since 1720 synonymously with pharmacy.

Buchheim was much impressed by the need of system if one wished to develop a science rather than accumulate a mass of unorganized information. He devised a system, partly chemical and partly biological, for the classification of medicinal agents and their "actions" in the body, which was set forth in three editions of his "Lehrbuch der Arzneimittellehre." [58] Although Buchheim was apparently intent on the need of order and system, he failed to make his a truly systematic classification. His group of drugs brought together under the heading "Glaubersalzes" cannot be considered a group of substances related in any way chemically to Glauber's salt, but a heterogeneous collection of substances which have as their one common property an ability to produce catharsis.

VIII. Gruppe des Glaubersalzes
Glaubersalz
Bittersalz
Schwefelsaures Kalium
Phosphorsaures Natrium
Weinsaures Kalium
Seignettesalz
Abführendes Brausepulver
Borazweinstein
Aethylschwefelsaures Natrium
Doppeltkohlensaures Magnesium
Citronensaures Magnesium
Mannit, Manna, Mannasyrup

Thus, we find at the very beginning of "Pharmacology" that although Buchheim made a contribution of enormous importance to medicine, he offered no solid foundation on which a new medical *science* could be built. Supposing the active principle of every plant, herb, and animal extract were known in pure chemical form and that these, as well as the several hundred thousand other chemical substances, had been arranged strictly according to some systematic chemical nomenclature, what use would such a classification be to medicine? If one did not know his pharmacology, how could one find an anesthetic, cathartic, or anthelmintic by looking in such a systematic, alphabetical list, an example of which is given below, taken from Dyson's "The Chemistry of Chemotherapy." [59]

α: α′-Dichloroisopropyl alcohol carbamic ester
3: 5-Dichlorophenyl arsonic acid
3: 8-Diethoxy-9-carboxylic acid
Diethylacetamide

Diethylamine
Diethylaminoacetonitrile
Diethylaminolactic nitrile
Diethylaminolactic nitrile methyl iodide
Diethylaminophenylacetonitrile
Diethyl aniline
Diethyl carbinol
1:1′-Diethylcarbocyanine iodide
Diethyl ether
Diethylglycine-p-amino-o-oxybenzoic acid methyl ester

Consider also our pharmacopoeia, which is arranged in the same manner. No one can use it without a previous knowledge of pharmacology. This is being recognized by the pharmacopoeial committee, which has issued a small booklet grouping the pharmacopoeial preparations under such headings as cardiac drugs, cathartics, antiseptics, anthelmintics. Furthermore, one cannot compare the "actions" of two or more drugs. How can the increase of blood pressure and respiratory rate produced by one substance be compared with the uterine contractions and diuresis produced by another? It is questionable if Buchheim's pharmacology allows the systematic treatment necessary for the development of a science.

The Error in Buchheim's Pharmacological Concept. Buchheim's first pupil was Otto Schmiedeberg, who, spared from the drudgery of reorganization and systematization and equipped with his splendid laboratory in Strassburg, stepped into this untouched field of pharmacology, free to carry on Buchheim's teachings. That he was well fitted for this opportunity was shown by the impetus which he gave to this subject and the founding of over 40 new departments in different parts of the world by his pupils, among whom were leaders in the medical profession. Pharmacology was greeted with a surprising wave of enthusiasm, but, even with the great productivity of these laboratories, doubt began to arise as to the status of pharmacology, and, in spite of all attempts to quell such fears, this doubt still exists.

Although Buchheim's emphasis on the experimental investigation of drugs and the need of system should receive nothing but praise, if we look at the matter without sentiment, it will be found that pharmacology differed in no way from pharmacy. The only way the pharmacist had to differentiate a "drug" from any other plant was to study its "action" in man or animals. True it is that these studies were not systematic, but the action in man of a great many drugs was known to us before Buchheim's time and much experimental work on the action of drugs in animals had been carried out in different laboratories. There was, therefore, nothing essentially new in the concept of pharmacology nor in its name. There was, however, the idea of systematizing our knowledge of the "action" of drugs, but this system failed even in Buchheim's own hands and that it was given up by his followers can be seen from the following brief review.

Schmiedeberg recognized that Buchheim's system and classification was impractical as well as unscientific. He was, however, unable to devise a

systematic classification of his own and, on this account, gave up a life-long desire to write a systematic textbook on pharmacology, publishing instead his "Grundriss der Pharmakologie"[60] for the aid of medical students and practitioners.

An analysis of the tables of contents of Schmiedeberg's book and those of his followers shows one common tendency, that is, to turn from Buchheim's idea of chemical headings to biological ones. The first chapter in Schmiedeberg's book, for example, is headed "The Nerve and Muscle Poisons"; the second, "Organic Substances Causing Local Irritation." Brunton,[61] although his book is a model of system of a sort, apparently realized the impossibility of a systematic chemical approach to the subject and went at it from all sides—chemical, botanical, zoölogical, pharmacological, and therapeutic. Meyer and Gottlieb's splendid book[62] is based entirely on a biological plan; in fact, they open their introduction to the first edition as follows: "Experimental pharmacology in the broadest sense deals with the reactions of living organisms to chemical substances or, to put the matter in another way, the behavior of organisms to changes in the chemical environment in which they live. Pharmacology is a part of Biology." They use, however, the same general mixture of tissue, organ, and function headings as did Schmiedeberg and Brunton. Sollmann,[63] who has perhaps done as much for pharmacology proper as anyone in this country, follows no systematic plan whatever, pharmacological, chemical, botanical, medical headings being used in no particular order—"The Pharmacology of Temperature Regulation," "Antimony," "Uranium," "Agranulocytosis," "Allergic Phenomena," and so forth. *We may safely conclude that after nearly one hundred years of pharmacology, there is no evidence of the "system" which Buchheim felt so necessary.* His idea of a systematic arrangement of drugs, under which one was to find their "actions," has gone almost entirely, and one finds instead that the pharmacologist is arranging drugs under some part or function of the body.

The Functions of a Pharmacologist. We have considered Buchheim's pharmacology, and with this in mind let us see what are the functions of a pharmacologist. These are set forth in a great many articles, but a brief outline of the table of contents of Sir Thomas Lauder Brunton's classical volume on "Pharmacology, Therapeutics, and Materia Medica"[61] will show them sufficiently well for our purpose. One cannot but marvel at the extent of Brunton's knowledge.

Brunton begins with a description of the chemical elements, their classification, and the general reactions between chemical substances and the body. He then goes on to the action of drugs on protoplasm, blood, and low organisms, moving on to their actions on higher invertebrates. After this, the actions of drugs on various parts of the body are taken up, such as those on muscle, nerve, spinal cord, brain and organs of special sense, and on functions as respiration. He then includes a chapter on methods of administering baths of all types, as well as massage, the stomach pump, and so forth.

After this, antidotes and antagonistic action of drugs are taken up. Then, under "Section II, General Pharmacy" we find all the pharmaceutical preparations; after this, a systematic survey of drugs in two parts: "Inorganic Materia Medica"—hydrogen, oxygen, sulphur, acids, metals, and so forth—arranged in a very systematic manner, and "Organic Materia Medica"—carbon compounds, fatty acid series, and aromatic series. This is followed by several chapters on "Vegetable Materia Medica," systematically arranged in "Sub-Kingdom I., Phanerogamae. Division I., Angiospermae; Class I., Dicotyledones Polypetalae; Sub-Class I., Thalamiflorae," and so forth. The animal kingdom is treated with equal care—classes of "Mammalia," "Aves," "Pisces," and orders of "Rodentia," "Pachydermata" under which comes "Lard." An index of diseases and remedies concludes the book. Here we find "Abscess" treated by alcohol, iodine, oakum, sheet lead, sodium auro-terchloride. The list includes all manner of diseases and symptoms, as acidity, acne, afterpains, and their treatment. If we add to this list serums, vaccines, pollens, vitamins, roentgen-rays, radium, and ultra-violet light, and, as some would have us, the hospital pharmacy, as well as a ward, the list is certainly formidable.

In view of the above, the following quotation from a letter to Professor Heubner seems particularly apt. This was written in 1938 by Sir Henry Dale, who has kindly given me permission to use it. "In general terms the question I raised was the necessity of discussing, *not* the necessity for pharmacologists, but the proper claims and the proper scope of Pharmacology, in view of the rapid changes already in progress in the aims and methods of therapeutics, and of the accelerated changes which I think can be foreseen in the near future. Unless something is done, the impression will grow, that Pharmacology is only a nebulous border-line between Biochemistry, Physiology, and Pathology, on the one hand, and Therapeutics on the other. My aim is certainly not to extinguish the Pharmacologist, but to secure his survival."

After the statements of Schmiedeberg, Meyer, Cushny, Dixon, and others that we are studying the "reaction of the organism to chemical substances," and the fact that whatever system there is in pharmacology does not use drugs as a basis, but some part or function of the organism, have we not already given up pharmacy or its analogue, pharmacology, and are we not in reality studying the organism rather than drugs?

The "Action" of Drugs versus the Reaction of the Organism to Drugs. In order to settle this philosophical question, it will be necessary to digress somewhat. We will assume that all things are of chemical nature, that they are made of two things only, electrons and protons, and that they differ only in the number and arrangement of these.

We will also consider for the sake of argument that drugs consist of single, pure, chemical substances. A drug is not a magical substance. We can never see a molecule, but we know it only by its reactions to other chemical substances. Its actions can, therefore, be nothing but its chemical

or physical properties or functions. These are fixed at the beginning by the number and arrangement of its electrons and protons. A drug's actions or reactions, behavior, or what one wishes to call it, in a test-tube reaction with other chemical substances, in the body of a man, turtle, or fish, is preordained; it is nothing but a chemical reaction (or a physico-chemical one) and could be predicted by a perfect chemist if he could know the chemical environment into which this substance was to enter. If his drug were hydrochloric acid and the chemical environment silver nitrate solution only, any high school student could predict the reaction. If, however, the drug were a complex organic substance about to enter even a test tube full of other organic substances, our best chemist would be utterly unable to predict what would happen, but merely from lack of knowledge. The theoretically perfect chemist could make such a prediction.

When we put a drug into a living organism, what are we doing? We start with a substance about which we supposedly know everything (which practically never is the case), and we put it into an almost limitless sea of chemical substances, many of utterly unknown nature. As we know our drug, our main interest lies in the unknown, that is, the human organism. We observe some response, as a change in rate of the animal's respiration. No one would dispute that this is the result of injection of the drug, but is it the "action" of the drug? I think not. The drug first came in contact with a certain chemical environment in the blood, certain cells, or body fluids. It reacted with one or more chemical substances of this environment or by its presence brought about a physico-chemical change in the environment, which in our present state of knowledge we are seldom able to unravel. This primary reaction was a purely chemical or physico-chemical one. It would have occurred anywhere, in any test tube or animal's body with exactly the same setup of chemical substances. The secondary changes, however, leading to nerve impulses, muscle contractions, and so forth, although of a chemical or physico-chemical nature, were not necessarily reactions with the drug but were due to *the specific chemical setup in this particular species of organism.* This particular architectural arrangement of chemical substances can be found nowhere else, except in another individual of the same animal species. Although everything that we know of must be of a chemical nature, as it is made of electrons and protons, the properties and functions of any specific organized group of chemical substances are dependent upon the architectural arrangement of the molecules of this group exactly as the properties and functions of a molecule are dependent upon the architectural arrangement of its atoms. A pig, a cow, and a bird might conceivably be made of the same chemical substances, but their number and arrangement give these particular agglomerations of electrons and protons properties of their own.

It is hoped that this illustration will be sufficient to make it clear that we are not studying drugs, as Buchheim realized. Their study is chemistry, pharmacy, or materia medica. We are not studying their "actions," which

apparently was not recognized by Buchheim, as their actions are chemical attributes of the drugs and belong in the field of general chemistry. We are instead studying the unknown, the human organism, a particular, complex agglomeration of chemical substances, and using chemical substances as tools with which to do this. One more illustration may be allowable.

$$Q \leftrightharpoons \begin{cases} A = \text{Color reaction} \\ B = \text{Precipitate} \\ C = \text{Formation of substance } x \text{ of known structure} \\ D = \text{Formation of substance } y \text{ of known structure} \\ E = \text{Formation of substance } z \text{ of known structure} \end{cases}$$

When one makes or discovers a new chemical substance, Q, in determining its composition and structure, one does not merely look at it, but arrives at a knowledge of its nature by *allowing it to react with known chemical substances,* as A, B, C, and so forth. By means of such reactions as in-

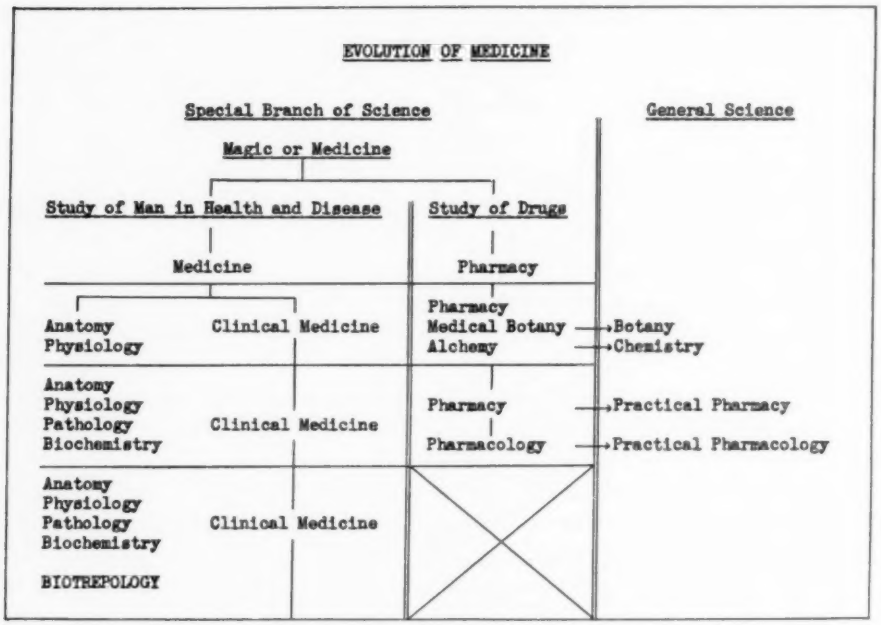

FIG. 1.

dicated above, one determines the character of the unknown substance, the structural arrangement of the different radicals, and so forth.

The age-old reactions between drugs and the body may be looked at in the same light. At first the body was used as a means of differentiating a drug from an inactive plant. Then chemistry was developed; drugs and chemical substances became the *known factors, and now we are studying the body by means of its reaction to these known chemical substances.*[64]

It is a method of unbelievable usefulness. By exposing the body to these substances, we will discover varieties of cells of which we are unaware. We will discover unknown functions of these, and finally those chemical substances of which the cells are built, as well as their ultra-microscopic arrangements. Such knowledge, arrived at by studying the reaction of the organism to chemical substances, automatically gives us that for which we are looking with which to build a systematic foundation for therapeutics.

The following diagram representing the evolution of medicine will serve to show how much came from the original "Medicine, Magic, or Pharmacy"; how very soon medicine split into two groups, one studying the body and the other drugs; how, when our knowledge developed, the magic went out of drugs; how they were seen to be chemical substances; and how their study led to the general science of chemistry. It shows the gradual development of the biological group which has ever since the start held together as an entity, simply subdividing into certain branches for convenience. But it is clear that those studying drugs never did belong to this group. Their interests were not primarily biological. One after another they left our medical schools and in many of these today pharmacology is nothing but a myth, having no department of its own, no special group for its study, originating nothing, and parasitically using the work of others as teaching material in order to conform to the insufficient requirements of our class "A" medical schools.

Part II. The Study of the Organism by Means of Its Reaction to Chemical Substances

In order to carry out such a plan systematically, the organism as a whole, as well as its various parts, must be considered. An outline of the factors involved is given below:

(1) Whole organism
(2) Systems, as the circulatory or respiratory
(3) Organs, as the eye and the spleen
(4) Unit building blocks of the organism, the cells
    (*a*) Structures, as nucleus, mitochondria
    (*b*) Systems, as gels
    (*c*) Unit building blocks of the cells, that is, molecules
(5) Extracellular chemical substances
    (*a*) Solutions—body fluids, as plasma, cerebrospinal fluid
    (*b*) Deposits, as bone, dental enamel
(6) Pathological tissue

Invading organisms to be considered individually.

Such an anatomical, rather than functional, outline may seem to many a strange basis for this plan, but a careful analysis will show that all function is reaction of some structure, whether of the whole organism, a system, cell, or molecule.

The measureable reactions of the whole organism are relatively few; changes in weight, height, metabolic rate are examples. The reactions of the whole organism occurring after exposure to chemical substances as alcohol, apomorphine, opium, are so complex that they do not allow simple recording as a whole and are usually broken down for analysis and one body function at a time considered. As, however, one will wish to find a description of the immediate as well as delayed response of the entire organism to each substance, these can be described under the *name* of the substance causing the response. The changes which take place in systems, as the respiratory, and in organs, as the eye, are so numerous that it seems unnecessary to treat them systematically. Blood pressure and respiration rate, for example, are changed by practically every known chemical substance. I have collected several thousand such reactions. They are the resultants of many factors. They are, however, facts and may be recorded under the name of the system, organ, or function in an alphabetical index.

Zoölogical Concept of Organism. Breaking down the organism still further, we come to what at first sight seems a very different class of body divisions, that is, the cells. These are the smallest biological units of which the organism is built; certain well-known types have been recognized and generally agreed upon, as nerve, muscle, and glands. It would seem logical as well as feasible to use cells as the basis of our study and to develop a cellular classification. Although general types of cells have long been recognized and much has been written about certain classes of cells, there has, to my knowledge, been no systematic attempt made to arrange the cells of any one species of animal as the zoölogist classifies animals, in phyla, classes, orders, families, and so forth, for purposes of study. The histologist has been interested in the spatial arrangement of the cells of the kidney. The physiologist is interested in the functional systems of the body and wishes to know the electrical diagram of the different nerve-muscle mechanisms, so to speak. When one uses a chemical substance for purposes of study, rather than the microscope or physical stimulation, this reaches at the same moment many types of cells in different parts of the organism. Whole classes, orders, or families of cells, as the case may be, will respond. *We are not, therefore, primarily interested in the geographical distribution of cells, but in the zoölogical classes of cells of which the body is built.* We do not wish to make the same mistake which Pliny did, who classified animals according to their place of abode, as flying animals, land animals, water animals; that is, we do not want to make geographical divisions of cells, as smooth muscle of the eye, the spleen, the vessels of the liver, when they may all be of exactly the same smooth muscle type. The difficulties of zoölogical classification are beautifully described in Hertwig's Manual of Zoölogy translated by Kingsley,[65] from which and other sources it would seem that zoölogical groups are arrived at by using all means at one's disposal—visual, functional, phylogenetical, paleontological, embryological, and so forth—and that the final criterion is the consensus of zoölogical

opinion. It would almost seem that the method adopted by Adam and Eve for naming the animals in the garden of Eden, described to me many years ago by Dr. William T. Councilman, might be the best for classifying and naming the cells of the body. "What shall we call this little thing?" said Eve. "Well, it looks like a toad and hops like a toad. Why not call it a toad?" replied Adam.

The zoölogists deal with individuals which are free to move about. We must deal with cells many of which are fixed in relation to other cells, and it is often difficult to know what is part of one or the other, as is the case with certain nerves and muscles. Then we are well aware that in reality there are no boundaries within the body. We consist of a shell of dead epithelium full of salt solution in which are the body cells, but these cells are chemical agglomerations bounded by chemical membranes and the whole immersed in a chemical solution. The cell is in equilibrium with the solution in which it lives, and so are all the other cells of the body. Thus no cell can exist alone, but is in balance with the rest of the organism. For practical purposes, however, we may consider cells as units. We shall probably do well to make too few rather than too many subdivisions of tissues, but with such fine methods of differentiation as those of reaction to chemical substances, we might almost be able to show that each cell in the body differs from every other. The cell again will be found to have its parts which correspond to the systems and organs of the body, and these are known to be built of molecules, which in turn are made up of atomic systems, below which we need not go.

It is, however, in the cellular units that I believe the greatest progress will be made. We have observed the cells both micro- and ultra-microscopically, and it is doubtful if we can go much further by visual means. However, by applying the methods used by the chemist in determining the invisible composition and structure of molecules, we may possibly discover the components as well as the invisible structure of the cell, as suggested above.

We will make use of every reaction at our disposal, regardless of type, but many of them will be gross reactions of the organism, as convulsions, change in respiratory rate, which can be easily seen; others, the appearance in the blood, urine, or expired air of substances not normally present; still others, intracellular reactions which will take elaborate means for investigation. But even if we cannot describe, after introducing into the organism a few molecules of acetylcholine, just what chemical reaction goes on in certain cells, we eventually discover which cells are primarily affected, and gradually discover a whole series of substances which produce this same response in these particular cells. From such data it is likely that some day someone will solve the riddle and tell us the substance or architectural chemical arrangement within the cell which primarily reacted with these substances to start the observable body response.

Extracellular Chemical Substances. Solutions, as the plasma, bile, cerebrospinal fluid, are not living substances. Many of them, as well as extracellular deposits, can be obtained in large enough amounts for direct chemical analysis. Data concerning changes which occur in such systems when exposed to chemical substances can be recorded under this heading alphabetically.

It is my purpose to point out the immensity of our problem of studying the reaction of the organism to chemical substances rather than with any thought of giving the impression that it is a simple matter. The problem is so great and we are so utterly unprepared for it that anything in the way of an actual proposal will seem absurd. However, a beginning must be made and the following outline will serve to illustrate a few points which will immediately come to mind.

THE HUMAN ORGANISM

I. NEURONS
- *A. Receptors*
  1. Olfactory
  2. Optic
  3. Gustatory
     - *a.* Of bitter taste
     - *b.* Of sweet taste
     - *c.* Of sour taste
     - *d.* Of salt taste
  4. Auditory
  5. Proprioceptive
     - *a.* Vestibular
       - (1) Labyrinthine
       - (2) Of semicircular canals
     - *b.* Of muscles, joints, and tendons
  6. Of tactile discrimination and stereognosis
  7. Of coarse touch and pressure
  8. Of pain
  9. Of temperature
     - *a.* For heat
     - *b.* For cold
  10. Of visceral reflexes
- *B. Coördinating Neurons,* especially the following groups (including synapses)
  1. Of sensation and consciousness
  2. Of contraction of skeletal muscle in voluntary movements
  3. Ocular
     - *a.* For accommodation
     - *b.* For pupillary constriction
     - *c.* For pupillary dilatation
     - *d.* For movements of extra-ocular muscles
  4. Glandular
     - *a.* For lacrimation
     - *b.* For salivation
     - *c.* For sweating
     - *d.* For secretion of mucus, digestive juices, etc.

5. Gastrointestinal
    a. For swallowing
    b. For vomiting
    c. For gastric and intestinal motility
    d. For defecation
6. Genito-urinary
    a. For bladder control
    b. For erection and ejaculation
    c. For uterine contraction
7. Cardiovascular
    a. For vasoconstriction
    b. For vasodilatation
    c. For cardiac inhibition
    d. For cardiac acceleration
8. Respiratory
9. Sympathetic regulatory
10. Parasympathetic regulatory
11. Heat regulatory

C. Effectors

1. Somatic (to skeletal muscle)
2. Visceral (preganglionic and postganglionic)
    a. Craniosacral (parasympathetic)
    b. Thoracico-lumbar (sympathetic)

II. Muscle Cells

A. Skeletal

1. Muscle fiber (sarcoplasm, myofibrillae)
2. Spindle fibers
3. Myoneural junction

B. Cardiac

1. Auricular
2. Ventricular
3. Nodal
    a. Sino-auricular
    b. Auriculoventricular
4. Purkinje tissue

C. Smooth

1. Uterine
2. Vascular
   Intestinal sphincters
   Radial of iris
3. Gastrointestinal
   Gall-bladder
   Bronchial
   Fundus of urinary bladder
   Circular of iris
   Ureteral

III. Gland Cells

A. Externally Secreting

1. Ceruminous
2. Sebaceous
    a. Of hair follicles
    b. Of Meibomian glands

3. Serous
   a. Lacrimal
   b. Sudoriparous
   c. Zymogenic
      (1) Salivary
      (2) Pancreatic
      (3) Fundic
      (4) Of Paneth cells
4. Mucous
   a. Of gastrointestinal tract
      (1) Salivary
      (2) Buccal
      (3) Of sinuses
      (4) Esophageal
      (5) Cardiac
      (6) Pyloric
      (7) Of Brunner
      (8) Columnar epithelial
      (9) Of gall-bladder and ducts
   b. Of genito-urinary tract
      (1) Urethral and para-urethral
      (2) Cervical
   c. Of respiratory tract
5. Of intestinal columnar epithelium (other than serous or mucous)
6. Of mammary gland
7. Renal
8. Hepatic (bile secretory)
9. Prostatic
10. Of ovary
11. Of testis

B. Internally Secreting

1. Pituitary
   a. Of anterior lobe
   b. Of posterior lobe
2. Thyroid
3. Parathyroid
4. Of islets of Langerhans of pancreas
5. Of suprarenal cortex
6. Of chromaffin tissue
   a. Of suprarenal medulla
   b. Of accessory bodies
7. Testicular
8. Ovarian
   a. Of corpus luteum
   b. Of Graafian follicle
9. Placental
10. Hepatic
11. Thymus
12. Pineal

IV. Integument Cells (Coverings and Linings)

A. Epithelial of skin and mucous membranes

1. Of skin
2. Of hair
3. Of nails

4. Of teeth (enamel organ)
6. Mucous membranes
    a. Ciliated
    b. Non-ciliated

B. Mesothelial

1. Peritoneal
2. Pericardial
3. Pleural
4. Of tunica vaginalis testis

C. Endothelial

1. Blood vascular
    a. Arterial
    b. Venous
    c. Capillary
2. Lymphatic vascular
3. Endocardial

D. Other Linings and Coverings

1. Dura mater
2. Pia mater
3. Synovial cavities and bursae
4. Of membranous labyrinth
5. Of anterior and posterior chambers of eye
6. Of renal glomerulus
7. Of renal tubules (for reabsorption)

V. Cells of Supporting Tissue

A. Of Connective Tissue

1. Collagenous
2. Elastic
3. Reticular
4. Adipose
5. Mucous (vitreous humor)

B. Of Bone

C. Of Cartilage

VI. Reproductive Cells

A. Male

1. Spermatogonia
2. Spermatocytes I and II
3. Spermatids
4. Spermatozoa

B. Female

1. Primitive ova
2. Oögonia
3. Oöcytes
4. Mature ova

VII. Hematopoietic Cells

A. Erythroblastic

1. Of bone marrow

B. Myeloblastic

1. Of bone marrow

C. Monoblastic

1. Of bone marrow
2. Of spleen

D. Lymphoblastic
1. Of bone marrow
2. Of spleen
3. Of lymph nodes
4. Of lymph nodules

E. Of Clasmatocyte Formation
1. Of bone marrow
2. Of spleen
3. Of lymph nodes
4. Of liver
5. Of connective tissue

F. Of Platelet Formation
1. Of bone marrow

VIII. Free Cells

A. Erythrocytes
1. Mature
2. Immature

B. Granulocytes
1. Mature
   a. Neutrophiles
   b. Basophiles
   c. Eosinophiles
2. Immature
   a. Myeloblasts
   b. Myelocytes

C. Lymphocytes
1. Mature
2. Immature

D. Monocytes

E. Clasmatocytes

F. Plasma Cells

IX. Extracellular Substances

A. Solutions
1. Plasma
2. Lymph
3. Intercellular fluids
4. Fluids of serous cavities
   a. Pleural
   b. Pericardial
   c. Peritoneal
   d. Of tunica vaginalis testis
5. Aqueous humor
6. Endolymph and perilymph (of the internal ear)
7. Cerebrospinal fluid
8. Synovial fluid

B. Deposits
1. Matrix of bone
2. Enamel
3. Dentine
4. Matrix of cartilage
5. Connective tissue fibers
   a. Elastic
   b. Collagenous
   c. Reticular

Common Parasites of Man

I. Animals Parasites of Man

A. Protozoa

1. Rhizopoda (Ameboid protozoa)
   - *a.* Endameba histolytica
   - *b.* Endameba coli
   - *c.* Endameba gingivalis
2. Mastigophora (Flagellates)
   - *a.* Leishmania donovani
   - *b.* Leishmania tropica
   - *c.* Trypanosoma cruzi
   - *d.* Trypanosoma gambiense
   - *e.* Trypanosoma rhodesiense
   - *f.* Trichomonas hominis
   - *g.* Trichomonas vaginalis
   - *h.* Trichomonas gingivalis
   - *i.* Giardia intestinalis
3. Sarcosporidia
4. Sporozoa
   - *a.* Plasmodium vivax
   - *b.* Plasmodium malariae
   - *c.* Plasmodium falciparum
   - *d.* Plasmodium ovale

   } Malaria organisms
5. Ciliata (Ciliates)
   - *a.* Balantidium coli

B. Spirochete

1. Treponema
   - *a.* Treponema recurrentis
   - *b.* Treponema pallidum
   - *c.* Treponema vincenti
   - *d.* Treponema pertenue
2. Leptospira icterohemorrhagiae

C. Platyhelminthes (Flatworms)

1. Trematoda (Flukes)
   - *a.* Schistosoma hematobium
   - *b.* Schistosoma japonicum
   - *c.* Schistosoma mansonium

   } Blood flukes
2. *Cestoda* (Tapeworms)
   - *a.* Diphyllobothrium latum
   - *b.* Hymenolepsis
     - (1) Nana
     - (2) Diminuta
   - *c.* Taenia
     - (1) Saginata
     - (2) Solium
   - *d.* Echinococcus granulosus (Hydatid disease)

D. Nemathelminthes (Roundworms)

1. Nematoda
   - *a.* Trichuris trichiura (Whipworm)
   - *b.* Trichinella spiralis (Trichina worm)
   - *c.* Strongyloides stercoralis
   - *d.* Ancylostoma duodenale
   - *e.* Ancylostoma braziliense
   - *f.* Necator americanus

   } Hookworms

g. Enterobius vermicularis (Human oxyurid)
h. Ascaris lumbricoides
i. Wuchereria bancrofti (Filaria bancrofti)
j. Onchocerca volvulus or O. caecutiens (Nodule filaria)
k. Loa loa (Eye worm)
l. Dracunculus medinensis (Guinea worm)

E. Arthropoda

1. Hexapoda (Insects)
   a. Calliophoridae larvae (Blowfly)
   b. Pediculus humanus (Body and head louse)
   c. Phthirius pubis (Pubic louse)
2. Arachnida (Ticks, mites)
   a. Dermacentor venustus (Tick)
   b. Sarcoptes scabiei (Scab mite)
   c. Demodex folliculorum (Hair follicle mite)
   d. Trombidiidae (Harvest mite)

II. Plant Parasites of Man

Thallophytes

1. Bacteria
   a. Cocci
      (1) Staphylococcus pyogenes
      (2) Staphylococcus epidermidis
      (3) Hemolytic streptococci
      (4) Non-hemolytic streptococci
      (5) Pneumococcus
      (6) Gonococcus
      (7) Meningococcus
   b. Bacilli
      (1) Bacillus influenzae
      (2) Bacillus Koch-Weeks
      (3) Bacillus pertussis
      (4) Bacillus ducreyii
      (5) Bacillus typhosus
      (6) Bacillus paratyphosus-A
      (7) Bacillus paratyphosus-B
      (8) Bacillus enteritidis
      (9) Bacillus aertrycke
      (10) Bacillus suipestifer
      (11) Bacillus dysenteriae
      (12) Bacillus coli communis
      (13) Vibrio cholerae
      (14) Bacillus mallei
      (15) Corynebacterium diphtheriae
      (16) Bacillus tuberculosis
      (17) Bacillus leprae
      (18) Brucella melitensis
      (19) Bacillus anthracis
      (20) Bacillus pestis
      (21) Bacillus tetani
      (22) Bacillus botulinus
      (23) Bacillus welchii
      (24) Bacillus tularensis
      (25) Bacillus of granuloma inguinale

2. Fungi
   - *a. Phycomycetes*
     - (1) Coccidioides
     - (2) Mucor
   - *b.* Ascomycetes
     - (1) Saccharomyces
     - (2) Cryptococcus
     - (3) Endomyces
     - (4) Monilia
   - *c.* Fungi imperfecti
     - (1) Oidium
     - (2) Torula
     - (3) Madurella
     - (4) Glenospora
     - (5) Sporotrichum
     - (6) Trichosporium
     - (7) Aspergillus
     - (8) Penicillium
     - (9) Scopulariopsis
     - (10) Microsporon
     - (11) Epidermophyton
     - (12) Endodermophyton
     - (13) Favus
     - (14) Actinomyces
     - (15) Leptothriceae
3. Disease agents of unknown relationships
   - *a.* Filterable viruses of
     - (1) Smallpox
     - (2) Encephalomyelitis
     - (3) Herpes zoster
     - (4) Herpes simplex
     - (5) Varicella
     - (6) Epidemic encephalitis
     - (7) Poliomyelitis
     - (8) Rabies
     - (9) Trachoma
     - (10) Molluscum contagiosum
     - (11) Warts
     - (12) Mumps
     - (13) Measles
     - (14) Dengue
     - (15) Pappataci
4. Rickettsia
   - *a.* Rickettsia prowazeki (Typhus)
   - *b.* Dermacentroxenus rickettsii (Rocky Mountain spotted fever)
   - *c.* Rickettsia quintana (Trench fever)
   - *d.* Tsutsugamushi disease

Such an outline gives us an oversight of the body, the types of tissue of which it is made, and some of the organisms with which it is at times infested. It is the type of arrangement which might be used in a course or book but not in a systematic index which would be arranged alphabetically.

I wish to thank those in our department who have so kindly put up with my attempts at reorganization, and also Dr. Sam L. Clark and Dr. Ernest W. Goodpasture for their very helpful advice and suggestions, as well as Dr. Herbert S. Wells, who spent much time on this when with us.

Indexing

At present we have no systematic method or place for recording the reaction of the organism to drugs. It is obvious that at some time this will become necessary and some system must be started, either in connection with some current index or as a separate (and costly) venture. Already certain tissues are known to be affected by hundreds of chemical substances as, for example, the various hypnotics and anesthetics, among which almost one thousand barbiturates alone have been made. In order to give an idea of how such a plan might be carried out, consider one type of tissue, muscle.

Tissue Types. Under any one tissue, as muscle, we find varieties, as cardiac, smooth, skeletal, and uterine. Under these main types, we may discover further subdivisions as shown in the case of smooth muscle. Just how such types of tissue will be named in the future is but one of our problems, but an important one.

Smooth Muscle

A. Contracts with epinephrine.	Relaxes with acetylcholine.
B. Relaxes with epinephrine.	Contracts with acetylcholine.
C. Contracts with epinephrine.	No response with acetylcholine.
D. No response with epinephrine.	Contracts with acetylcholine.
E. Contracts with epinephrine.	Contracts with acetylcholine.

Tissue Properties and Functions. Under any one type of tissue we may list alphabetically its properties, functions, or other information which we wish, as indicated.

Reaction to Chemical Substances. Having discovered the specific response of a function of one type of tissue, the reference to the work proving this may be recorded by placing the name of the substance under the proper tissue function and giving the reference after this.

Animal Used. Recording the type of animal used in each entry obviates a whole separate classification for each species. Tissues not occurring in man, as the nictitating membrane of the cat, can be added to the list of tissues, giving the name of the species after it.

Method. One of the most pressing needs of the pharmacologist today is what might be called a pharmacological analysis. What pharmacologist has at his fingertips the methods necessary to study the reaction of the tissues here outlined to any new drug? By recording with each entry the method used, one would automatically have such an outline. If the drug were of interest, as producing local anesthesia, one could look under nerve, sensory neurones of pain, and find a list of drugs already used and references to the methods by which these results were obtained.

Chemistry. In rare instances we know that certain chemical substances within the cell react with drugs to which the cells are exposed; for example, oxyhemoglobin reacts with carbon monoxide, the oxygen being replaced by the latter. In the same way, glutathione reacts with arsenic. In such cases we may record these reactions under " Chemistry," giving first the substance contained in the cell and, under this, the substance which reacts with it.

Pathological Conditions. Pathological tissue can be treated exactly as other tissue, and it would seem unnecessary to set aside a separate section for such discussion. In the case of recording the effect of digitalis in congestive heart failure on the contractility of pathological heart muscle, we would look under cardiac muscle, pathological conditions, then under that function in which we are interested—contractility, and under this place the substance, digitalis, followed by the response produced, together with a reference.

MUSCLE

Cardiac

Chemistry

Metabolism depressed by

Arsenic: reacts with glutathione. Voegtlin, Dyer and Leonard: U. S. Public Health Reports, 1923, xxxiii, 1882.

Distribution

Heart only

Functions

Conductivity decreased by

Ephedrine: (dog and rabbit) electrocardiographic studies. Chen and Meek: Jr. Pharmacol. and Exper. Therap., 1926, xxviii, 31.

Contractility increased by

Digitalis: (dog) optical recording of intraventricular pressure. Wiggers and Stimson: Jr. Pharmacol. and Exper. Therap., 1926, xxx, 263.

Irritability decreased by

Acetyl-β-methylcholine: (man). Starr: Am. Jr. Med. Sci., 1933, clxxxvi, 330.

Refractivity increased by

Quinidine: (turtle) muscle strips. Wedd: Am. Jr. Physiol., 1934, cviii, 265.

Rhythmicity

Rate increased by

Caffeine: (rabbit) perfused heart. Heathcote: Jr. Pharmacol. and Exper. Therap., 1921, xvi, 327.

Innervation

Sympathetic: cardiac branches of the stellate ganglia, few fibers directly from second to fourth thoracic ganglia.

Parasympathetic: cardiac branches from the vagi.

a. Fibers from right vagus mainly to the sinus node.

b. Fibers from the left vagus to the auricular ventricular node.

Internal conducting system: Purkinje fibers and nodal tissue. The left auricle is apparently without this system.

Structure
Cells are large, cross-striated; arise from a syncytium but in the adult there are intracellular discs; are branched and fibrils run from one to another. Nuclei are centrally located.
Pathological Conditions
Contractility
Congestive heart failure
Digitalis: (man) returned to normal as shown by x-ray. Stewart et al.: Arch Int. Med., 1938, lxii, 569.
Irritability
Chloroform
Epinephrine: (dog) increased to fibrillation. Levy: Heart, 1913, iv, 319.

Secondary Reactions. Obviously, it is not enough to know about the reaction of the organism to epinephrine, that vascular smooth muscle contracts after its injection. One wants to know what actually happens to the blood pressure, heart rate, blood volume, and to the animal as a whole. *This can never be known except by a systematic study of the reaction of the individual parts of the organism and the resultant secondary reactions.* There will be countless secondary reactions which may or may not have been analyzed which are, however, facts and can be recorded as, for example, blood pressure and respiration rate which are affected by practically every known substance. It is self-evident that if one wants the entire picture of the organism's reaction this will be found under the name of the substance producing the reaction which will necessitate a chemical index arranged according to one of the accepted chemical methods. Here one can record everything about the drug as is done in books on lead and on sulfanilamide.

Discussion and Conclusions

We have seen that the original pharmacists, medicine men, or magicians discovered the magic of life in chemical molecules, that as everything is made of these molecules, we are all studying chemistry in one form or another. There are, however, two main groups of " chemists," those studying the science of chemistry, the structure and properties of the chemical substances, and those studying special chemical agglomerations, that is, living plants and animals, or inanimate structures.

The medical group has existed for thousands of years as a special entity. They are not general biologists or chemists but have one purpose only, that is, to study the human organism in health and disease. The pharmacists, on the other hand, split off from this group early, as shown in figure 1, and studied drugs and later chemical substances. The interests of the pharmacist or chemist are not those of the medical man. He does not belong in the medical group; he has never been at home there as the pharmacist or as a teacher of materia medica.

Pharmacology has been shown to differ in no way from pharmacy. It arose from Buchheim's misconception that we can have a medical group

studying the "action of drugs." One must choose and study the drugs or the human organism, but one cannot make a science of the vacuum between the two. That our interest lies in the human organism and not in drugs has been demonstrated by the writings of practically all of Buchheim's followers. In spite of the general realization of this, pharmacology is still considered and taught as a study of drugs and their actions. One reason for this is the lack of any systematic method of studying the reaction of the body to drugs. Without system we have no science, and pharmacology today is not a science but merely a practical study of certain substances without system or order.

By considering the organism as a community of cells which can be arranged in classes regardless of location in the organism, we have suggested a systematic method of studying the reaction of the organism to chemical substances, as well as a method for recording our data in a systematic manner.

If that medical group known as pharmacologists would give up the study of drugs and study the body by means of its reaction to chemical substances, using these as his tools, he would be able to develop a systematic medical science and, in so doing, *would give us the information necessary for the building of a sound basis for rational therapeutics.*

Whether one starts with a *single drug* and studies the reaction of the organism to it, or with the organism and studies its reaction to a *single* chemical substance, makes no difference; but the end result of studying hundreds of thousands of chemical substances and their "actions," present-day pharmacology, and studying the human organism systematically by means of its reaction to chemical substances will be found to be very different things and to have far-reaching consequences. Ten years' experience with the latter method has convinced me of this.

Everyone will use this method of studying the body by means of its reaction to chemical substances. This is as it should be, but it is the function of our group only, to systematize this knowledge, to arrange the tools for use by others, and to be the custodian of that immensely important group of facts, namely, the means by which we can initiate, depress, or change specific functions of the organism.

The industrial chemist, pharmacist and/or pharmacologist will be of ever-increasing aid to the medical group. They will not only make new chemical substances, but they will want to know the reaction of the organism to *their particular product.* This will necessitate investigation, the need of trained men, and the very pressing need of the proper recording of our data. Where would the chemists be financially if they had no way of knowing what substances have already been made? We have at present only the crudest possible methods of finding those substances to which a given tissue reacts.

From this discussion it is suggested that the medical profession realize that the study of drugs, their actions, pharmacy, or its analogue phar-

macology, is not a true medical science; that we complete the long evolution of pharmacy by divorcing it as well as pharmacology from medicine and developing a new medical science differentiated from the other branches of medicine by the tools and methods which it uses, namely, the study of the human organism by means of its reaction to chemical substances.

Space will not allow a consideration of how such a plan of studying the body should be taught. The relationship of materia medica, pharmacy, pharmacology, prescription writing, dosage, toxicology, chemotherapy, and therapeutics has been discussed at length in the numerous articles referred to above, and it is the author's intention to outline in more detail the actual application of such a plan in a future communication.

Names may do good or evil. The name "Pharmacology" has certainly led us astray for nearly one hundred years. Any name which would divorce such a group as described above from pharmacy and describe a truly medical science would answer our purpose. "Biotrepy" or "Biotrepology" is suggested, from *bios,* life, and *trepo,* to change, or even "Chemobiotrepy."

After the revolutionary discoveries of the sulfonamides, great interest will be shown in studying "drugs" and great sums of money expended in such investigations; but the discovery of ether, as well as that of Salvarsan, although by no means insignificant, failed to put pharmacology on a sound basis. After thousands of years of experimentation, when it has been finally demonstrated beyond doubt that we cannot only relieve, but cure disease by the use of drugs, it would seem time to consider seriously the matter of the proper organization of this most important branch of medicine.*

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* Since this paper was read, the following statement appeared in "The Rockefeller Foundation, A Review for 1938" by Raymond B. Fosdick: "Though no subject in medicine would seem more important than pharmacology, which deals with the action of drugs and their use in disease, this field of medicine is hampered by lack of adequate financial support. In twenty-five recognized American medical schools there are no separate departments of pharmacology, the subject being combined for economic reasons with physiology or biochemistry. In many other schools where there is a separate division, the subject receives but meager support. This situation is doubtless responsible for the failure of pharmacology to attract recruits and for the shortage of outstanding younger men to fill professional chairs which are becoming vacant. Larger support is needed not only to promote fruitful research in this important field but also to improve the teaching on the applied side—the administration of drugs—which is notably weak in most American medical schools."

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CASE REPORTS

HICCUP AS A COMPLICATION OF ACUTE CORONARY ARTERY OCCLUSION*

By Morris M. Weiss, M.D., F.A.C.P., *Louisville, Kentucky*

Hiccup as a complication of an acute coronary artery occlusion is not mentioned in the literature. In the past year I have encountered this annoying and distressing symptom in three cases. In one patient the hiccups commenced about four hours after the onset of the painful features of the occlusion and lasted with varying severity for five days. In the other two cases they appeared on the second day following the occlusion and lasted, also with varying intensity, two and four days respectively. In one patient they ceased suddenly and in the others gradually subsided. Two of the patients had an uneventful recovery from the cardiac infarction. The other died with recurrent attacks of pulmonary edema two days after the hiccups had ceased. While the hiccups were extremely weakening and interfered with proper rest, it is difficult to consider their presence a contributing cause of the death of this patient because, aside from having had hypertension and angina pectoris for many years, he had had a previous coronary occlusion six months before the fatal attack.

Treatment was of no avail in abolishing the hiccups. All the usual remedies gave only temporary relief. Sedatives and opiates were of value in lessening the force of the diaphragmatic spasms and alleviating the resultant soreness of the chest and abdominal muscles. The results from the inhalation of 5 per cent carbon dioxide in oxygen were variable and not constant. In one patient who obtained relief on three separate occasions from its use, the carbon dioxide the fourth time caused cessation of audible cardiac activity for approximately two minutes. In view of the harmful results in individuals with heart disease from induced oxygen want,[1, 2] carbon dioxide should be cautiously administered and then only in low concentration.

The cause for the hiccups in these patients is obscure. Constitutional diseases such as diabetes or uremia were not present. All intra-abdominal factors were eliminated. Particular attention was paid to proper intestinal and urinary bladder evacuation. Local pressure was not a factor. There was no evidence that they originated from disease of the central nervous system. It is possible that an infarction of that portion of the ventricle resting on the diaphragm with resultant diaphragmatic irritation was responsible. A localized pericarditis with irritation of the phrenic nerve is also to be considered. Hiccup accompanying pericarditis has been mentioned in the literature.

Summary

Three cases of acute coronary occlusion complicated by hiccups have been encountered in the past year. The cause is obscure. They have no apparent prognostic significance. Treatment is disappointing.

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PRIMARY JEJUNAL ULCER; REPORT OF A CASE WITH RUPTURE AND RECOVERY *

By F. EUGENE ZEMP, M.D., F.A.C.P., *Columbia, S. C.*

PRIMARY jejunal ulcer is a very rare condition and differs in its clinical manifestations considerably from ulcers involving other parts of the gastrointestinal tract. Richardson [1] collected 12 cases in 1922. In 1933 Ebeling [2] made a survey of both domestic and foreign literature and presented a summary of the important findings in 47 collected cases and reported a case of his own. Since then Puhl,[3] and Hall [4] have each reported one case. Each case thoroughly studied, should add to its clinical entity.

CASE REPORT

E. B. R., a white male, 59 years of age, complained of pain in the lower abdomen. The family history was negative. He had had the usual childhood diseases, and typhoid fever at the age of 10. Twenty years ago he had experienced a severe case of diarrhea, which lasted three weeks and was undiagnosed as to etiology. There had been no operations or injuries. He drank four or five cups of coffee a day, occasionally tea, coca colas, and cocktails, and smoked rather heavily, consuming about 30 cigarettes a day. He slept well, but was of a nervous temperament and easily upset. He had lost 14 pounds during the past year.

The present illness had begun nine years ago, with pains in the lower abdomen, which were spasmodic in character and occurred at varying intervals. During the past five months they had been very severe and had caused him considerable discomfort. They were described as "a hurting" and "colicky-like," and occasionally there would be a gnawing or burning sensation in the epigastric region, not related to eating. Lying on his stomach gave some relief, and complete relief from a few days to a week or more occurred at various intervals. His appetite was good and there was no nausea or vomiting, but considerable gas with distention. Although constipated most of the time, he occasionally had a watery stool. Immediately after a bowel movement, his abdomen often became distended, especially if a laxative had been taken.

On physical examination he was 6 ft. 1½ inches tall, weighed 142 pounds, and was somewhat pale. His scalp, ears, and nose were negative. The pupils were normal in size and shape, and reacted promptly to light. There was no exophthalmos or icterus. The eye grounds were negative. His teeth were false. The examination of the throat was negative. There were no enlarged glands in the neck, but in the isthmus of the thyroid gland was a small hard nodule about the size of a marble. The chest was well developed; expansion was good, and the lungs were clear. There was no enlargement of the heart, and its action was normal. The blood pressure was

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132 mm. of mercury systolic and 70 diastolic. The abdomen was slightly scaphoid in shape, soft and relaxed, and no masses were palpable. The abdominal aorta was palpable, and descending colon contracted. The liver edge could not be felt, and there was no tenderness over the gall-bladder area. The spleen was not palpable, and nothing abnormal was felt in the kidney regions. The extremities were normal in size and shape. All reflexes were active and normal. The brachial arteries felt somewhat thickened. The genitalia were normal, except for a slightly enlarged epididymis. The prostate gland was firm, and the left lobe was slightly larger than the right. Proctoscopic examination revealed a normal mucous membrane.

In the laboratory studies the red blood cells were 3,890,000, hemoglobin 78 per cent, white blood cells 7,400 with 69 per cent polymorphonuclear leukocytes. The Wassermann and Kahn tests were negative. The urine had a specific gravity of 1.012, dark amber, acid, and did not contain any albumin or sugar. The microscopic study was normal. In the fractional gastric analysis the free hydrochloric acid ranged from 40 degrees to 70 degrees, and the total acids from 60 degrees to 78 degrees. On May 1, 1937, the examination was completed with a fluoroscopic study of the chest, stomach, and duodenum. The findings were normal, except for a moderate ptosis. A roentgen examination of the genito-urinary tract was also normal.

My impression, after the examination, was that there was a moderate visceroptosis with gastric hyperacidity, and probably an ulcer, very small or not demonstrable. He was, therefore, placed on an ulcer diet with the usual alkalies. Slight improvement followed for two weeks, at which time visible peristaltic waves were noted in the mid-abdomen. Because of this, a barium enema was given which was negative. He continued treatment, but did not improve. On May 20, 1937, the visible peristaltic waves were more prominent, and he complained of colicky-like pains in the lower abdomen with distention. An exploratory operation was advised, as a tumor of the small intestine was suspected, due to the mild obstructive symptoms. One week later, on May 6, 1937, he was taken suddenly ill with severe pains throughout the abdomen. Examination revealed a board-like rigidity with tenderness throughout. He was sent immediately to the Columbia Hospital. His temperature was 101° F., pulse 125, and blood pressure 110 systolic and 62 diastolic. The white blood cells were 7,500 with 84 polymorphonuclear leukocytes. A preoperative diagnosis of perforated duodenal ulcer was made; and that afternoon he was operated on by Dr. George Bunch. There was a segment of the upper jejunum that was red and congested with the omentum partially adherent on one side, and at this point an acute perforation was found of an antimesenteric ulcer about eight inches below the ligament of Treitz. The peritoneal cavity and the pelvis contained a ropy mucoid exudate. The ulcer was infolded with interrupted linen sutures, and a tag of freed omentum unattached was sutured over the closure. A large drain was inserted and the wound closed.

During the postoperative period the distention was relieved by a Levine tube for five days, and he was given glucose intravenously and by hypodermoclysis daily. At the end of six days he was placed on an ulcer regime, and left the hospital on July 10. He continued to improve and has not had any symptoms of importance up to the present time. On August 1, 1938, the jejunum was thoroughly studied by fluoroscopic and roentgen-ray examination, and there was no evidence of the ulcer or of any abnormal findings.

In conclusion, I wish to suggest as an aid to diagnosis, the more use of the five hour barium meal fluoroscopically in the non-perforated cases and the roentgenogram in the erect position in the perforated cases. The former frequently shows a dilatation of the jejunum proximal to the lesion with regurgitation of the barium and the latter an air bubble under the diaphragm.

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MINOR INJURIES OF THE CERVICAL SEGMENT OF THE SPINE AND THEIR CONSEQUENCES

Case Report *

By Alfred Gordon, F.A.C.P., *Philadelphia, Pennsylvania*

The majority of recorded cases of injuries of the cervical spine are instances of gross damages, such as dislocations or fractures of the vertebrae with secondary gross lesions in the spinal cord, leading to muscular atrophies or spastic paralysis of the extremities as the result of tracts—degeneration, with involvement of the sphincter of the bladder and occasionally, in males, persistent priapism. Cases of less severe damage are not common and frequently are not recognized. The cord symptoms in such cases are at first very slight; the moderate initial disability is looked upon with no special concern and the prognosis is ordinarily considered very favorable for a complete recovery. Nevertheless close and prolonged observation will reveal that the apparently mild disturbances have for an underlying basis serious lesions in the cord itself. As an example of such apparently minor lesions demanding recognition and serious consideration, the following case is reported.

Case Report

P. M., aged 50, a laborer, was driving a truck in October 1936, when the horse became frightened, ran off at a high speed and hit a pole. The driver was thrown off; the vertex of his head struck the ground, producing excessive anterior flexion of the cervical spine. There was no loss of consciousness, the patient was merely "dazed." During the following two weeks there was gradual development of pain in the neck and weakness in both arms. The patient was admitted to Coatesville Hospital where the head was immobilized and kept in an apparatus during eight weeks. After the removal of the latter, the patient was unable to move his head in any direction, could not raise his left arm above the shoulder and was troubled by muscular twitchings in both arms.

Upon examination at that time, the following condition was found: Roentgenological examination of the cervical vertebrae showed no fracture and no dislocation, but the intervertebral space between the sixth and seventh vertebrae was a little wider on the right than on the left side. The neck was rigid and no flexion, extension, rotation, or lateral movements could be obtained without causing considerable pain. The left arm could be raised only partially, although the shoulder-joint presented no evidence of damage (the roentgen-ray of the joint was negative and the head of the humerus could be rotated in the cavity without difficulty). There was apparently no atrophy of the muscles of the arms and no reactions of degen-

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Patient presented at the April Meeting of the Philadelphia Neurological Society.

eration could be obtained. The grip of both hands was good. The biceps and triceps reflexes on both sides were at times greatly diminished, and usually were unobtainable. By percussing the lower end of the radius on the left side, a slight flexion of the fingers was sometimes induced. This is the so-called "inversion reflex of the radius," characteristic, according to Babinski (1910), of an injury of the fifth cervical segment of the spinal cord. The third striking symptom in this case was continuous muscle-waves (myokymia) and fibrillary contractions of the flexors and extensors of both upper arms, more on the left than on the right side. The myokymia would become more pronounced upon mechanical irritation of the same muscles. Moreover, at times simultaneously with the clonic manifestations there were also sudden tonic spasms of the muscles of the forearm, but only on attempts to carry out abrupt voluntary movements. Finally it was observed that the scapulo-humeral tendon reflex was more marked on the left than on the right side. Percussion of the middle of the inner border of the scapulae produced abduction and external rotation of the entire arm, more on the left than on the right side. All forms of sensation were normal in the upper extremities.

The tendon reflexes of the lower extremities were increased, but there were no pathological reflexes. The sphincters had never been affected since the accident. The pupils also had been normal. Blood and urine were normal in every respect. The Wassermann test was negative and the spinal fluid was normal.

The patient's further course showed complete restoration of the function of the cervical muscles and considerable improvement in raising the arms. The objective pathological symptoms at present are: difficulty of obtaining tendon reflexes in the upper extremities; the occasional presence of "inversion of the radial reflex"; and finally continuous muscle-waves and fibrillary contractions of the muscles of both upper arms.

Comment

The muscular phenomena observed here belong to the large group of myoclonias. Several clinical types have been described: (*a*) Para-myoclonus multiplex, in which there is a simultaneous involvement of many muscles of the body; (*b*) Unverricht's type of myoclonus, in which myoclonic contractions are intensified by physical exertion and emotional stimuli and are associated with epilepsy; (*c*) Lundborg's type, in which clonic and tonic muscular contractions take place during an emotion, an embarrassment, and upon the slightest sensory stimulation (psychoclonic, psychotonic and sensoclonic reactions respectively); (*d*) myotonoclonic type of Popoff, in which clonic phenomena, during voluntary movements, are followed after a long interval by tonic muscular contractions; (*e*) Lenoble-Aubineau's type (nystagmus-myoclonia) which is characterized by simultaneous spasmodic twitchings of the muscles of the extremities and of the eye-globes associated with tremor of the head and is a familial disease in which are also found physical stigmata of degeneration; (*f*) the myoclonic post-encephalitic sequelae with or without typical parkinsonism, the muscular contractions of which may affect any part of the body including the palate, pharynx, uvula and even the diaphragm; (*g*) "acute infectious myoclonus multiplex," described by Hunt, characterized not only by myoclonic twitchings, but also by general signs of an infectious nature, such as fever, headache, pain at each myoclonic paroxysm and delirium; (*h*) finally myoclonia which manifests itself in the form of muscle-wave (myokymia) and fibrillary contractions.

Irrespective of the variety, all forms of myoclonia are characterized by the common symptom of paroxysms of involuntary and irregular clonic contrac-

tions of groups of muscles. The case described above belongs to the last clinical type. The wave-like muscular phenomenon (myokymia) combined at times with fibrillation, especially upon mechanical stimulation, is limited here to the flexor and extensor group of muscles in the upper arms, more on the left than on the right side. Considering the association of this symptom with the history of trauma in the cervical region of the spine, one is gradually led to the question of the pathogenesis of the myokymia.

Various authors have expressed divergent views concerning the origin of myoclonic dyskinesias. The so-called muscular view, according to which the phenomenon is myopathic in origin, is not satisfactory, particularly in cases of the type recorded here. Wagner-Jauregg's theory of a causal disturbance in the function of the thyroid and parathyroid glands cannot be applied to all cases of myoclonia. The explanation of the phenomenon on an exclusively psychogenic basis (hysteria, etc.) is equally unsatisfactory in most instances; in fact, the majority of authors believe in an organic origin of all cases of myoclonic twitchings. Friedreich was the first to hold such a view. He considers the muscular phenomena due to irritation of the cells of the anterior horns. The same view is held by Hunt. The very few cases that have come to autopsy have shown a variety of pathological findings. Saoli found slight degeneration in the upper segment of the cervical cord and a lipoid mass in the dentate nucleus of the cerebellum. Some authors believe that myoclonia is due to irritation of the motor cortex, but they have no autopsies to substantiate such a view. Roger, following Hunt, considers rhythmical myoclonia as a disorder in the striatal system and arrhythmical myoclonia due to a disorder in the spinal cord.

The case described in this contribution suggests strongly an anatomical disorder in the cervical cord. The continuous wave-like muscular contractions associated with fibrillations, also the occasional tonic spasms, all confined exclusively to the flexor and extensor groups of muscles, speak eloquently in favor of a continuous irritation of the segments of the cord innervating those muscles or of the nerves distributed in them, namely the musculo-cutaneous and the musculo-spiral nerves which originate in the fifth and the seventh cervical segments, respectively. Moreover, if we recall the presence at times of "the inversion of the radial reflex" on the left side, which, according to Babinski, is due to a damage of the fifth cervical segment, we are fortified in the assumption that the case under consideration is due to an anatomical disorder in the cervical cord. Babinski has also found that abolition of reflexes in the upper extremities indicates a cord lesion extending from the fifth to the eighth cervical segments.

As to the nature of the lesion in our case it can not be a destruction of the anterior horn cells, as otherwise there would have been muscular atrophy and flaccid paralysis, which are not present. The myokymia is here incessant and continuous. This motor phenomenon is therefore very probably due to an equally incessant and continuous irritation of the cells of the anterior horns or of the anterior roots. It developed soon after a brief preliminary period of paralysis of both upper extremities, following a forced flexion of the head.

Conclusion

The case under consideration is one of those very few recorded in the literature, which calls attention to the fact that fractures and displacements of the component parts of the cervical vertebrae, which are easily recognized, are

not the only structural damage requiring prompt intervention. Cases with less dramatic objective manifestations demand equally prompt and serious consideration.

The literature on the subject is meager. Jefferson calls special attention to the fact that in all such cases the injury may be trivial and it is directed against the head, producing extreme forward flexion. In a more recent interesting study Walshe and Ross report six cases, in which the cord symptoms were present, following excessive flexion of the head, and in which at the time of the injury the entire attention was given to the trauma of the head and none to the cervical spine. In their cases the changes in the tendon reflexes were the most conspicuous symptoms, and the roentgenography revealed no fracture or dislocation of the vertebrae, except in one case, in which there was a marked narrowing of the fifth, sixth, and seventh cervical intervertebral spaces.

In the case here reported there was also forced flexion of the neck with violence to the vertex of the head; there was no fracture or displacement of the cervical vertebrae but the intervertebral space between the sixth and seventh was a little wider on the right than on the left side. In addition to the changes in the tendon reflexes there was an unusual cord symptom, which was not observed in the cases recorded in the literature at my disposal: namely a myoclonic phenomenon in the form of myokymia and muscular fibrillation. In instances of apparently minor traumatism to the cervical spine the development of myokymia and its limitation to a distinct muscular group of the upper extremities innervated by the fifth, sixth, and seventh cervical segments indicates organic nerve injury.

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EDITORIAL

THE EXCHANGE OF CHIEFS OF SERVICE

EXCHANGE professorships at universities exist now in all countries, and their advantage is universally recognized. The chief of a hospital service is the analogue in the clinical field of the professor in the academic field. Would there not be many advantages to a system of exchanges of chiefs of services?

Just as a college exchanges professors for a while with some other college, so could a hospital exchange temporarily with another in its city one of its chief physicians or surgeons. A physician responsible for the organization and the conduct of a service in a hospital could thus spend a period of time every once in a while at an institution other than his own, taking over the work of the man for whom he has been exchanged. Osler recommended that a physician take one year out of every five as a sabbatical year, away from his usual work. Most persons, because of economic conditions, cannot absent themselves so long and so often. By means of such exchanges, however, a physician can be brought into completely new hospital surroundings every once in a while, and his associates by their contact with a new chief can also be given the stimulation of a new mental environment. Whether the period of exchange should be a short one, as a month, or a long one as a year, and what the frequency should be with which exchanges are made with another institution, are matters which would have to be decided between the individual hospitals. Some would want to have the periods of exchange made frequently and for long duration, some would deem it best to have the exchanges made but infrequently and for but short periods. There can be no general rule as to what is best for all.

The advantages of such an exchange to the hospitals concerned seem obvious. A hospital service loses the supervision of its chief for but a relatively short time. In return for this loss it has working within its walls a new man, an individual who during his stay will instill many fresh ideas into his new colleagues, both those on his own immediate staff, and those in other departments whom he meets as a result of consultations. In the course of years in all institutions certain procedures become routine and almost a habit. It is a natural tendency of man to get into a rut of routine, and once in such a rut he is apt to become slipshod in his work. With the introduction of a new chief the old routines and ideas are brought into review and inevitably compared with procedures and beliefs current in other places, and as a result of this reëxamination all profit, the staff of the hospital, the routine of the hospital, and medical relations in the city at large.

Provincialism, the feeling that the members of one's own hospital are the only ones well versed in medicine and the various specialties, will be overcome as the work of men from other places is seen and found good.

Esprit de corps will not be limited to the confines of one's own institution but will tend to spread and include the members of the hospitals with which exchanges are being made; and finally perhaps some day all physicians of the city will feel towards one another that same respect, friendship, and intimacy, that they now have for the staff of their own institution. Doctors will learn by direct contact and observation the special abilities not only of the men in their own group but the particular abilities of men in other hospitals in that locality.

The exchange physician will frequently find that his new associates are especially well versed in lines of work with which he has not been particularly concerned up to now. Thus it may be that they are especially skilled in gastroscopy or in the study of arthritis. His own special interests in the past may have been along different lines. In such cases he cannot but learn and profit from his contact with these younger men on his staff. He will not be giving them his experience without receiving a fair return. Perhaps he will find in his new hospital several junior physicians expert in some particular line of work, for instance parasitology, which may be quite an undeveloped field in his own institution, and he could well request permission to take back with him to his hospital one of this group, to the benefit of the young man and to the benefit of the institution to which that young man is transferred. On the other hand, the exchange physician may be especially interested in something which is studied and treated but little at his new place of work. Thus, for instance, he may be an authority on tuberculosis, and as a result of his presence and stimulation a whole new field may be opened up to and developed by the men with whom he now comes in contact.

The plan here presented is not entirely new. At the Peter Bent Brigham Hospital in Boston a step in this direction has already been made, in that for some time past it has been customary there for men unconnected with the institution to be invited to act as Attending Physicians pro tem., and to conduct rounds for a period of two weeks or so. What has been done at Peter Bent Brigham is excellent. It is capable of widespread application.

I. H. Marcus.

REVIEWS

Physical Diagnosis. By RICHARD C. CABOT, M.D., and F. DENNETTE ADAMS, M.D. 12th Ed. 846 pages; 16 × 23.5 cm. Williams and Wilkins Co., Baltimore. 1938. Price, $5.00.

The twelfth edition of Cabot's Physical Diagnosis, published by Richard C. Cabot and F. Dennette Adams, shows many changes from the earlier editions. These were strongly marked with the personality of the author and based to a great extent on his personal experience. In the preparation of the present volume a large number of specialists drawn principally from Cabot's colleagues in the Massachusetts General Hospital have collaborated. Such a development has manifest advantages and will probably add to the popularity of this well known text.

No field of physical diagnosis has been neglected and all are well presented. The many new photographs and roentgen-ray pictures deserve note because of their careful selection and excellent reproduction without loss of detail. The diagnostic charts are valuable.

There is an adequate and well balanced chapter on elementary electrocardiography and another new chapter on the nervous system which is excellent.

In brief, the new edition has retained the greater part of the value of the older text and shows many new features which will greatly help the modern medical student.

R. B. M., JR.

Trauma and Disease. Edited by LEOPOLD BRAHDY, B.S., M.D., and SAMUEL KAHN, B.S., M.D. 613 pages; 14 × 23 cm. Lea and Febiger, Philadelphia. 1937.

An exceptionally well selected group of contributors has enabled the editors to present a picture of the relation of trauma to disease which is of great interest to all internists. To those physicians who are concerned with the determination of compensation for trauma it will be invaluable.

There is a very sane introductory chapter by the two editors, in which the requisites for allocating a causative rôle to trauma are analyzed. This is followed by chapters on the relation of trauma to heart disease, peripheral vascular disease, pulmonary disease, gastrointestinal disease, genito-urinary disease, obstetric and gynecologic conditions, mental disorders, neurosyphilis, diseases of the nervous system, of the bones, of the joints, of the spine, neoplasms, diabetes, thyroid disease, and septicemia.

The bibliography is arranged topically and placed at the end of each section. Most of the authors present valuable articles from the foreign literature which is on the whole richer in this field than our own.

The method of treatment of the subject, as might be expected, varies in the different chapters. The chapter on the relation of trauma to the diseases of joints, for example, approaches the problem in a broad theoretical manner which however interesting it may be will not be of great help in connection with the analysis of the rôle of trauma in an individual instance. In contrast the discussion of the effect of trauma on disease of the spine is admirably specific and fortified by case citations and brief summaries of the author's conclusions.

All in all, this monograph is a very valuable contribution in a difficult field and every internist who consults it will wish to have a copy on his own shelves.

M. C. P.

Crystalline Enzymes. By JOHN H. NORTHROP. xv + 176 pages; 16 × 23.5 cm. Columbia University Press, New York. 1939. Price, $3.00.

This excellent monograph is based on a series of lectures on the isolation and chemistry of the proteolytic enzymes and bacteriophage, which were given at Columbia

University in 1938. Although the historical development of the subject has been given adequate attention it is primarily a review of the author's own experimental work.

The contents consist of seven chapters devoted, respectively, to the general chemistry of enzymes; pepsin; pepsinogen; chymo-trypsinogen and chymo-trypsin; trypsinogen, trypsin and trypsin-inhibitor; carboxypeptidase; bacteriophage, and finally, an appendix containing detailed directions for the preparation and crystallization of the enzymes.

The book is written in a very interesting manner and contains many valuable tables. The photomicrography of the crystalline enzymes is particularly excellent.

E. G. S.

The New-Born Infant. By EMERSON L. STONE, M.D. 291 pages; 20.5 × 13.5 cm. Lea and Febiger, Philadelphia. 1939. Price, $3.00.

The purpose of this publication is expressed in the preface: "The death rate of infants from seven days to one year of age, in the United States registration area, has been reduced 53 per cent during the years of 1916 to 1934 inclusive. During the same time the death rate of infants under seven days of age has been reduced only 10 per cent." Naturally any work concerned with furthering a reduction in infantile mortality is of interest to the obstetrician, pediatrician and general practitioner.

The author has devoted himself extensively to the physiology, the development and the medical care of the newly born infant. Such pertinent subjects as injuries attendant upon delivery and infections and disorders of the special systems receive full attention.

The entire manual is well organized, presenting conflicting views in an unbiased fashion. The work is short and yet without any serious omissions. At times the author seems to overstep his scope, especially when discussing feeding.

There are excellent bibliographical references included.

The book is unreservedly recommended for the student, obstetrician, pediatrician, and general practitioner.

J. E. B.

Recipes and Menus for Allergics: A Cookbook for the Harassed Housekeeper. By MYRA MAY HAAS, and NATHAN SCHAFFER, M.D.; Menus by CAY HILLEGAS, B.S. 250 pages, 7 drawings; 20.5 × 14 cm. Dodd, Mead and Company, New York. 1939. Price, $2.50.

The task of preparing diets for an allergic, who must avoid one or more foods, is no sinecure, as anyone who has attempted it will readily agree. This is an especially formidable undertaking when such basic dietary elements as wheat, eggs or milk must be withheld and unfortunately, they are among the more common offenders. The authors would seem to have succeeded rather well.

In the preface, a brief but good explanation of the meaning of allergy is given; also, there is a listing of certain substances as cottonseed, cereals and spices with comments upon the many food products of which they may be constituents. In addition, the content of mixed foods as sauces and dressings, beverages and flavorings and colorings are discussed.

The diet section is divided into eight parts: egg allergy, milk allergy, wheat allergy and combinations of these. The final section has to do with miscellaneous food allergies such as coffee, fish and spices.

Seven of the sections are preceded by amusing drawings by Soglow which are a real addition to the text.

In the reviewer's opinion, the book should be most helpful to both patient and physician when allergic elimination diets are indicated.

H. M. B.

COLLEGE NEWS NOTES

New Life Member

Dr. Clarence L. Hyde, F.A.C.P., Akron, Ohio, became a Life Member of the American College of Physicians on May 31, 1939.

Gifts to the College Library

Acknowledgment is made, with appreciation, of the receipt of the following donations to the College Library of publications by members:

Books

Dr. Richard M. Burke (Associate), Sulphur, Okla., "A Historical Chronology of Tuberculosis";
Rear Admiral Charles S. Butler, F.A.C.P., (MC), U.S.N., "Syphilis Sive Morbus Humanus: A Rationalization of Yaws So-Called" (College Edition).

Reprints

Dr. Mitchell Bernstein, F.A.C.P., Philadelphia, Pa.—6 reprints;
Dr. J. Lewis Blanton, F.A.C.P., Fairmont, W. Va.—1 reprint;
Dr. Samuel Blinder (Associate), New York, N. Y.—1 reprint;
Dr. William J. Bryan, Jr., F.A.C.P., Tulsa, Okla.—1 reprint;
Dr. Richard M. Burke (Associate), Sulphur, Okla.—1 reprint;
Dr. Herbert R. Edwards, F.A.C.P., New York, N. Y.—1 reprint;
Dr. Paul C. Eschweiler (Associate), Brooklyn, N. Y.—1 reprint;
Dr. K. D. Graves (Associate), Roanoke, Va.—2 reprints;
Dr. W. R. Hallaran (Associate), Cleveland, Ohio—1 reprint;
Dr. C. H. Hofrichter, F.A.C.P., Seattle, Wash.—1 reprint;
Dr. LeMoyne Kelly (Associate), New York, N. Y.—2 reprints;
Dr. J. Roderick Kitchell (Associate), Philadelphia, Pa.—1 reprint;
Dr. D. N. Kremer, F.A.C.P., Philadelphia, Pa.—1 reprint;
Dr. Sidney F. LeBauer (Associate), Greensboro, N. C.—1 reprint;
Dr. D. O. N. Lindberg, F.A.C.P., Decatur, Ill.—1 reprint;
Dr. Ross M. Lymburner, F.A.C.P., Hamilton, Ont.—2 reprints;
Dr. Willard Machle (Associate), Cincinnati, Ohio—2 reprints;
Dr. Clifford W. Mack, F.A.C.P., Livermore, Calif.—1 reprint;
Dr. H. M. Margolis, F.A.C.P., Pittsburgh, Pa.—1 reprint;
Dr. A. Park McGinty (Associate), Atlanta, Ga.—2 reprints;
Dr. Fred N. Miller (Associate), Crater Lake, Ore.—1 reprint;
Dr. Charles F. Nichols, F.A.C.P., Philadelphia, Pa.—1 reprint;
Dr. S. T. Nicholson, Jr., F.A.C.P., Pottstown, Pa.—1 reprint;
Dr. Frank Garm Norbury, F.A.C.P., Jacksonville, Ill.—1 reprint;
Dr. William Ogden, F.A.C.P., Toronto, Ont.—1 reprint;
Dr. F. R. Park (Associate), Bala-Cynwyd, Pa.—1 reprint;
Dr. Arthur J. Patek, F.A.C.P., Milwaukee, Wis.—1 reprint;
Dr. Carleton B. Peirce, F.A.C.P., Montreal, Que.—1 reprint;
Dr. Johannes F. Pessel, F.A.C.P., Trenton, N. J.—1 reprint;
Dr. Henry Pleasants, Jr., F.A.C.P., West Chester, Pa.—2 reprints;

Dr. Raymond J. Reitzel, F.A.C.P., San Francisco, Calif.—2 reprints;
Dr. Philipp J. R. Schmahl, F.A.C.P., New York, N. Y.—1 reprint;
Dr. Christopher C. Shaw (Associate), Bellows Falls, Vt.—1 reprint;
Dr. J. J. Singer, F.A.C.P., Los Angeles, Calif.—3 reprints;
Dr. Neuton S. Stern, F.A.C.P., Memphis, Tenn.—1 reprint;
Dr. Merritt H. Stiles (Associate), Philadelphia, Pa.—4 reprints;
Dr. Harold Sugarman (Associate), Saskatoon, Sask.—1 reprint;
Dr. C. R. Thomas, F.A.C.P., Chattanooga, Tenn.—1 reprint;
Dr. Kilby P. Turrentine (Associate), Kinston, N. C.—1 reprint;
Comdr. W. H. H. Turville, F.A.C.P., (MC), U.S.N.—1 reprint;
Dr. Walter I. Werner (Associate), Albuquerque, N. M.—2 reprints;
Dr. Elihu S. Wing, F.A.C.P., Providence, R.I.—1 reprint;
Dr. E. B. Winnett, F.A.C.P., Des Moines, Iowa—1 reprint;
Dr. Bernard Langdon Wyatt, F.A.C.P., Tucson, Ariz.—7 reprints;
Dr. L. S. Ylvisaker, F.A.C.P., Newark, N. J.—1 reprint.

Acknowledgment is also made of the gift by Dr. O. Costa Mandry, F.A.C.P., San Juan, P. R., of the bound numbers of the Bulletin of the Department of Health of Puerto Rico, Volumes I, II, and III, containing contributions by several members of the College.

Dr. William Gerry Morgan, F.A.C.P., Historian of the College, presented for the College Archives a photograph of a formal luncheon of Officers of the College and selected guests, given during the Montreal Annual Session of the College by Dr. J. E. Dubé, F.A.C.P. Dr. Morgan also donated to the College twenty-eight volumes from his personal library, including among others the following:

Cyclopedia of American Medical Biography, I & II—Howard A. Kelly;
Notes on Chemical Lectures—John Marshall;
The Mechanism of the Heart and Its Anomalies—Emilie Geraudel, translated by Louis F. Bishop, Sr., F.A.C.P., and Louis F. Bishop, Jr., F.A.C.P.;
Lambe on Cancer—William Lambe (1809);
Life and Letters of Dr. William Beaumont—Jesse S. Myer;
Mechanisms of Character Formation—William A. White;
The Destiny of Man—John Fiske;
The Memoirs of a Physician—Alexandre Dumas.

American Board of Internal Medicine Examinations

The next written examination by the American Board of Internal Medicine is scheduled for October 16, 1939, to be given in various centers. For specific information address the Secretary-Treasurer, Dr. William S. Middleton, 1301 University Ave., Madison, Wis.

Dr. Walter E. Vest, F.A.C.P., Huntington, W. Va., President of the Southern Medical Association, received the honorary degree of Doctor of Science at the recent Commencement Exercises of the Medical College of Virginia.

At the recent meeting of the Society for Clinical Investigation held at Atlantic City, N. J., Dr. E. M. Landis, F.A.C.P., Phillips Medalist of the College, was appointed Secretary. Dr. J. Q. Griffith (Associate), Philadelphia, was elected a member of the Society.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., addressed a joint meeting of the Lackawanna County Medical Society and the Scranton Dietetics Society, in Scranton, on Tuesday, April 18, 1939, on "Deficiency Disease with Special Reference to Vitamins."

Dr. Conley H. Sanford, F.A.C.P., has been appointed Professor of Medicine and Chief of the Division of Medicine in the College of Medicine of the University of Tennessee, effective July 1, 1939. Dr. Sanford also becomes Chief of Staff of the John Gaston Hospital as of the same date.

Dr. Theodore F. Bach, F.A.C.P., Associate in Medicine, University of Pennsylvania Graduate School of Medicine, spoke before a Seminar of The Hazelton Branch of the Luzerne County Medical Society, Thursday, May 18, 1939, on "Diagnostic Points of Value, together with, Treatment of Arthritis with Methods Available to the General Practitioner."

On January 11, 12, and 13 of the current year, the Rochester Academy of Medicine, under the Presidency of Dr. David B. Jewett, dedicated its new home. Among the honorary guests were distinguished physicians and surgeons from all parts of the United States and Canada. President Jewett presided at the Dedicatory Meeting, the Dedicatory Dinner, and the Public Meeting. Dr. William A. Groat, F.A.C.P., President of the Medical Society of the State of New York, and Dr. Logan Clendenning, F.A.C.P., Kansas City, Mo., were among those presenting addresses.

At the recent annual meeting of the Gastro-Enterological Association the following officers were elected for the coming year: President, Dr. Irvin Abell, Louisville, Ky.; First Vice-President, Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill.; Second Vice-President, Dr. Russell S. Boles, F.A.C.P., Philadelphia, Pa.; Secretary, Dr. Albert F. R. Andresen, F.A.C.P., Brooklyn, N. Y.; Treasurer, Dr. A. H. Aaron, F.A.C.P., Buffalo, N. Y.; Recorder, Dr. Sara M. Jordan, F.A.C.P., Boston, Mass.; Members of the Council, Dr. Chester M. Jones, F.A.C.P., Boston, Mass., Dr. Ralph C. Brown Chicago, Ill., and Dr. Ernest H. Gaither, F.A.C.P., Baltimore, Md.

The next meeting of the Association will be held June 10–11, 1940, at the Hotel Claridge, Atlantic City, N. J.

The Twelfth Graduate Fortnight of the New York Academy of Medicine will be held October 23 to November 3, 1939, on the subject of "The Endocrine Glands and Their Disorders." The program will comprise Afternoon Clinics, Evening Meetings, Morning Round Table Conferences, and Scientific Exhibits. The registration fee for non-members is $5.00. Among the invited speakers on the Evening Sessions program appear: Dr. J. B. Collip, F.A.C.P., Montreal, "Physiology of Anterior Lobe of Pituitary Gland"; Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis., "Therapeutic Application of Female Sex Hormones"; Dr. David Marine, F.A.C.P., New York, N. Y., "Physiology and Principal Inter-relations of the Thyroid"; Dr. James H. Means, F.A.C.P., Boston, Mass., "Hypothyroidism"; Dr. Robert F. Loeb, F.A.C.P,. New York, N. Y., "Adrenal Insufficiency"; and Dr. B. S. Oppenheimer, F.A.C.P., New York, N. Y., "The Cushing Syndrome. Neoplasms of the Adrenal

Gland." Program and Registration folders may be obtained from the Secretary, 2 East 103rd St., New York, N. Y.

Lt. Col. A. Parker Hitchens, F.A.C.P., of the Medical Corps, U. S. Army, has been appointed to head the Department of Public Health and Preventive Medicine at the University of Pennsylvania School of Medicine, Philadelphia, Pa. In addition to directing this Department, Col. Hitchens will become the George S. Pepper Professor of Public Health and Preventive Medicine.

Col. Hitchins graduated from the Medico-Chirurgical College of Philadelphia in 1898, and for a number of years was connected with the H. K. Mulford Laboratories. From 1925 to 1929 he was technical adviser in public health and sanitation on the staff of Gen. Leonard Wood in the Philippines. More recently, Col. Hitchens has been assistant professor of military science and tactics at the University of Pennsylvania.

At a recent meeting of the American Medical Association, Dr. Rock Sleyster, F.A.C.P., Wauwatosa, Wis., was inducted as President, Dr. Nathan B. Van Etten, F.A.C.P., New York City, was elected President-Elect, and Dr. Alphonse McMahon, F.A.C.P., St. Louis, was elected Vice-President.

The program of the Third Annual Tuberculosis Seminar of Asheville, N. C., July 10–16, 1939, shows the following participation by Fellows of the American College of Physicians: Dr. Karl Schaffle, F.A.C.P., Asheville, Chairman of the Seminar; Dr. William Ray Griffin, F.A.C.P., Asheville, Address of Welcome; Dr. A. B. Craddock, F.A.C.P., Asheville, "The Minute Anatomy of the Lung and the Development of the Tubercle (Illustrated)"; Dr. Charles H. Cocke, F.A.C.P., Asheville, "History, Symptoms and Examination of the Patient" and "The General Principles of Medical Treatment"; Dr. S. M. Bittinger, F.A.C.P., Black Mountain, "Demonstration of Artificial Pneumothorax, Under Fluoroscopic Control"; Dr. Walter R. Johnson, F.A.C.P., Asheville, "Tuberculosis of the Gastro-Intestinal Tract"; Dr. Paul H. Ringer, F.A.C.P., Asheville, "The Selection of Patients for Collapse Therapy (Illustrated)" and "Non-Tuberculous Pulmonary Diseases (Illustrated)."

Dr. Bradford J. Murphey, F.A.C.P., Director of the Child Guidance Clinic at Wilkes-Barre, Pa., received the honorary degree of Doctor of Science at the Colorado College Commencement, recently.

Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., addressed the Section on Gastroenterology of the Medical Society of New Jersey at its 173rd Annual Meeting, at Atlantic City, June 8, 1939, on "The Constitutionally Inadequate Patient." Dr. Manfred Kraemer, F.A.C.P., Newark, N. J., retired as the Chairman of this Section and Dr. Hyman I. Goldstein (Associate), Camden, N. J., retired as the Secretary of this Section and was elected Chairman. The New Jersey Medical Society is the oldest medical society in America.

Erwin F. Faber, anatomical artist and instructor in pathological drawing at the University of Pennsylvania School of Medicine, died during May of a heart attack

at his home in Philadelphia. His illustrations for important medical works are widely known to the medical profession.

A Request for Suggestions

In the Board Room of the College Headquarters, 4200 Pine Street, Philadelphia, there is a wall space above the mantle, 43 inches broad and 36 inches high, which offers a splendid opportunity for an original painting or etching.

The Board Room is finished in oak paneling and the proposed painting will be the highlight of the room.

The House Committee desires suggestions from the membership at large in order that an appropriate and dignified work of art may be selected. One subject might represent some event in the development of medicine, preferably occurring in North America. Another possibility might be found in some historical event of importance in connection with the origin and growth of The College.

The House Committee will appreciate suggestions regarding the type and subject of the proposed picture. It will also be receptive to offers from any member who desires to underwrite same.

Communications should be addressed to the Chairman of the House Committee, Edward L. Bortz, M.D., 2021 W. Girard Avenue, Philadelphia, Pennsylvania.

Special Meeting of the Board of Regents

Joint Conference Between the Board of Regents of the American College of Physicians and the Board of Trustees of the American Medical Association

At the invitation of the Board of Trustees of the American Medical Association a joint conference between that Board and the Board of Regents of the American College of Physicians was held at Chicago, April 29, 1939, at which there was an extended discussion of graduate, postgraduate, and continuing medical education and a detailed review of the activities of the Council on Medical Education and Hospitals of the American Medical Association. Following the conference there was a special meeting of the Board of Regents at the Drake Hotel, Chicago, at which resolutions were adopted, (1) instructing Dr. Hugh J. Morgan, as Chairman of the Committee on Postgraduate Education of the College, to attend a joint session of the Council on Medical Education and Hospitals and representatives of the American Board of Internal Medicine at St. Louis on May 14, 1939, and (2) appointing the Committee on Postgraduate Education of the College, consisting of Drs. Hugh J. Morgan, Charles Sidney Burwell, Joseph A. Capps, Charles H. Cocke, and William J. Kerr, to meet and confer with the Council of Medical Education and Hospitals of the American Medical Association, or a committee from this organization, for the discussion and formulation of principles and plans for the further development of graduate medical instruction.

Other items of business transaction by the Board of Regents included an announcement from President O. H. Perry Pepper that Dr. Howard T. Karsner of Western Reserve University School of Medicine had accepted the appointment as General Chairman of the 1940 Annual Session, Cleveland, of the College and that the official date would be April 1–5, 1940. Dr. Karsner had already proceeded with the tentative appointment of committees and other general arrangements. Hotel

Statler has been selected as the official Headquarters Hotel, but General Sessions and Round Tables will be conducted in the public auditorium.

Dr. William D. Stroud, Treasurer, presented the following additions required for the 1939 operating budget of the College, which upon resolution were approved:

Counsel Fee, House Committee's appeal for exemption from real estate taxes on College Headquarters	$ 167.35
New typewriter for Editor's office	93.56
Additional appropriation for traveling expenses of guest speakers, New Orleans Session, President's budget	750.00
Total	$1010.91

Treasurer Stroud also pointed out that there may develop the necessity for an additional appropriation to cover expenses of the Ladies Entertainment Committee, New Orleans Session, because the College budget was prepared with the supposition that there would be only 250 visiting ladies, whereas 578 were registered. There was a general discussion concerning the ladies entertainment for future Annual Sessions of the College and the consensus of opinion was that these programs should be less elaborate in the future. A resolution was adopted providing that the Treasurer and the Executive Secretary be authorized to pay any proper bills that may be received for the ladies entertainment at the New Orleans Session, should the present appropriation be inadequate.

The President was directed to communicate to the American College of Surgeons a report that the American College of Physicians has been carrying on conferences and appointing representatives, but has taken no decisive action on its future policy with regard to the problem of graduate and postgraduate medical education.

On the recommendation of the Committee on Public Relations, presented by Dr. James E. Paullin, Chairman, resignations of Dr. Charles S. Greene (Associate), Canton, Ohio, and Dr. Ralph Henry Kuhns (Associate), Chicago, Ill., were accepted. Likewise by resolution, action was taken concerning the remittance of dues of a Fellow who had retired from practice because of illness, and a hearing of another Fellow concerning discipline. The Secretary General, Dr. George Morris Piersol, reported the following deaths since the last meeting of the Regents:

Dr. Alfred Stengel, Master, Philadelphia, Pa., April 10, 1939;
Dr. Amos Henry Stevens, Fellow, Fairmont, W. Va., March 12, 1939.

Dr. Piersol reported that Dr. Alexander G. Brown, Jr., of Richmond, Va., had become a Life Member of the College.

President Pepper called upon members of the Board of Regents either to volunteer to give papers personally at the next Annual Session or, by letter, to suggest the most competent men who might be obtained as speakers. He also asked for suggestions of general topics that may have been neglected in recent years, also suggestions for the Convocation orator.

The meeting adjourned with all Officers and Regents standing in silent tribute to the memory of Dr. Alfred Stengel.

MINUTES OF THE BOARD OF GOVERNORS

New Orleans, La., March 27, 1939

A regular meeting of the Board of Governors of the American College of Physicians was held at New Orleans, March 27, 1939, with Dr. Charles H. Cocke presiding as Chairman, and Mr. E. R. Loveland acting as Secretary, and with the following present: Dr. Oliver C. Melson, Dr. Ernest H. Falconer, Dr. Fred M. Smith, Dr. W. S. Kerlin (representing Dr. J. E. Knighton), Dr. Henry R. Carstens, Dr. A. Comingo Griffith, Dr. Clarence L. Andrews, Dr. Charles H. Cocke, Dr. Julius O. Arnson, Dr. Alexander M. Burgess, Dr. Paul K. French, Dr. J. Morrison Hutcheson, Dr. Charles E. Watts, Dr. Walter E. Vest, Dr. Hugh A. Farris, Dr. Joseph Kaufman (representing Dr. Charles F. Moffatt), Dr. Fred W. Wilkerson, Dr. Fred G. Holmes, Dr. Lewis B. Flinn, Dr. Turner Z. Cason, Dr. James G. Carr, Dr. C. W. Dowden, Dr. Eugene H. Drake, Dr. Henry M. Thomas, Jr., Dr. Louis H. Fligman, Dr. LeRoy S. Peters, Dr. Charles F. Tenney, Dr. A. B. Brower, Dr. Homer Rush (representing Dr. T. Homer Coffen), Dr. M. D. Levy, Dr. James F. Churchill, Dr. James J. Waring, Dr. Francis G. Blake, Dr. Samuel E. Munson, Dr. Robert M. Moore, Dr. Thomas Tallman Holt, Dr. William B. Breed, Dr. Warren Thompson, Dr. Leander A. Riely, Dr. Nelson G. Russell, Dr. Edward L. Bortz, Dr. John L. Calene, Dr. J. Owsley Manier, Dr. Louis E. Viko, Dr. Arthur Duryea (representing Dr. Harry L. Arnold), Dr. J. Howard Holbrook, and Dr. Thomas Parran.

Chairman Cocke announced that proper credentials as Alternates had been presented by Dr. W. S. Kerlin, of Louisiana, Dr. Joseph Kaufman, of the Province of Quebec, Dr. Homer Rush, of Oregon and Dr. Arthur Duryea, of Hawaii, and that in accordance with the By-Laws they were properly seated with all rights and privileges of Governors.

The Secretary read abstracted Minutes of the preceding two meetings of the Board of Governors held in New York City during 1938, which were approved with the correction that Dr. C. W. Dowden had been elected Vice Chairman of the Board of Governors and not "reëlected."

Chairman Cocke addressed the Board of Governors, calling to their attention that the subject for particular consideration by the Governors and Regents at the current meeting was that of postgraduate instruction, referring also to the joint meeting and dinner of the Regents and Governors, the night preceding at the Roosevelt Hotel, New Orleans.

The Secretary read communications from various Governors who were unable to be present, and reported that Dr. J. E. Knighton, Governor for Louisiana, had been prevented from coming because of the tragic death of his son.

On motion by Dr. Walter E. Vest, seconded and regularly carried, it was

RESOLVED, that the Secretary immediately dispatch a message of sympathy to Dr. J. E. Knighton from the Board of Governors.

At the request of Chairman Cocke, the Secretary distributed the report of the Committee on Credentials on candidates for Fellowship and Associateship, and the action of the Board of Regents in regard to their election. Full lists of those recommended were passed among the Governors for reviews. The Secretary reminded the Governors that the By-Laws and regulations of the Regents state that proposals and material must be filed thirty days in advance of election, so that the Credentials Committee may have adequate time to complete its work.

Chairman Cocke supplemented the Secretary's remark in regard to the thirty-day rule, emphasizing its importance and the impossibility of the Credentials Committee acting upon proposals that arrive late, and for which there has not been adequate time to collect the prescribed data. Chairman Cocke also emphasized the

importance of Governors writing full and detailed letters in connection with the endorsement of candidates. The Credentials Committee must know why the Governor feels the candidate is qualified, and data should be given in detail, both from the personal and professional standpoints.

The Secretary, Mr. Loveland, was then called upon to present the list of Associates who would be automatically dropped from the Roster because of failure to qualify for Fellowship within the five-year period, in accordance with the By-Laws. Not only was a mimeographed list, with the names alphabetically arranged, presented to each Governor, but each case was discussed, so that the Governors would be fully informed. Eighty-two per cent of those elected to Associateship five years previously had qualified for Fellowship.

Chairman Cocke predicted that any of these men who had completed their five-year Associate term and who may later have adequate credentials for Fellowship may be proposed directly for Fellowship, credit to be given by the Credentials Committee for their five-year Associate term already completed.

Dr. Cocke also reported that the Regents had instructed the Credentials Committee to draw up a new booklet, outlining the requirements, and to more specifically and clearly state the requirements.

On questions propounded by Dr. Thomas T. Holt, Chairman Cocke advised that while a favorable amount of credit is at present being extended for certification by the American Board of Internal Medicine, the Credentials Committee has no right to exempt any candidate for Fellowship from the regular requirements of the Constitution and By-Laws. However, Dr. William B. Breed, Governor for Massachusetts, and a member of the Credentials Committee, stated that modification of the requirements was under consideration by the Board of Regents.

The Secretary, Mr. Loveland, then presented a mimeographed list of Fellows and Associates who were delinquent in dues for two or more years, and who, according to the By-Laws, were subject to being dropped from the Roster. The Governors were asked to scrutinize the list and to communicate with any members in their respective territories, if they felt such members should be further encouraged to retain their memberships—a period of sixty days' grace would be extended to these men by the Board of Regents.

Chairman Cocke announced to the Board of Governors that since the last annual meeting, there had been lost through death 29 Fellows and 4 Associates; that there had been added to the Life Membership Roster, 16, bringing up the total to 117 Life Members of which 8 have died since original subscription, leaving a balance of 109.

The Secretary reported, at the request of the Chairman, that the membership Roster showed

2	Masters
3,027	Fellows
1,202	Associates
4,231	Total

Chairman Cocke made a report on the Postgraduate Courses offered under the auspices of the College during the two weeks just preceding the current Annual Session; 2 Courses given in Baltimore, 2 Courses in St. Louis and 1 Course in Chicago. Two of the scheduled Courses in Chicago and one Course in Nashville had to be cancelled because of inadequate registration. The Courses given had proved very popular, with a total attendance of 118. Indications were that members want specific, intensive courses in the particular branches in which they are interested, rather than general courses. Dr. Cocke suggested that the Board of Governors might assume as one of its functions the investigation through members in their

respective districts of the desires and needs of the members in regard to the type of courses to be offered next year. It was brought out in the discussion that there was a slight increase in the number of members who registered for the Postgraduate Courses for 1939 over the number who registered for the courses in 1938. The registration showed that members came from thirty-four States of the United States, from Canada and Hawaii.

Dr. Henry M. Thomas, Jr., Governor for Maryland, discussed the two Courses given at Baltimore under the organization and leadership of Dr. Pincoffs. He expressed the opinion that the College could profit from year to year by more carefully studying the experience of the previous years and the experience at the various places where Postgraduate Courses have been given, and he suggested that the College appoint an individual, or committee, to supervise the organization of these courses, giving suggestions for improvement to those offering new courses and to ascertain what courses are preferred. He further suggested that the Secretary mail to each Governor the name or names of College members who pursued these courses from each State.

Chairman Cocke said that Governor Thomas' suggestion would be carried out, but that the Committee on Postgraduate Education of the College would serve as the clearing house for suggestions, for organization, selection and improvement of Postgraduate Courses in the future.

Governor Thomas made the further suggestion that each member of the class each year should be given a complete Roster, including names and local addresses of men taking the courses, so that contacts among the members could be facilitated.

Dr. Fred G. Holmes, Governor for Arizona, opened the discussion as to the possibility of holding Postgraduate Courses at another time of year than just before the Annual Session. It so happens that physicians in the southwest are at the peak of their work in March and April, and it would be far more convenient for them to take the graduate courses later in the spring, or in the early autumn.

Chairman Cocke advised that the members had been carefully canvassed in this regard, and while there were many factors to be considered, including the convenience of the teaching institutions where the courses are given, it had appeared that the period immediately preceding the Annual Sessions suited the largest number of members, although the matter might be further considered with respect to giving two sets of courses, each at different seasons.

Governor Thomas T. Holt, of Kansas, recommended that courses be announced in subjects such as physiology, chemistry and metabolism, in order that a larger number of men might avail themselves of the opportunity of building up knowledge in these subjects, which is so needed. He suggested that where courses are oversubscribed, the teachers might be persuaded to repeat the courses again later in the year.

In the discussion that followed, the following questions were advanced: Do some members utilize these Courses but fail to attend the Annual Session which follows? What influence has the location of the annual meeting exerted on the attendance of graduate courses in cities not in fairly close proximity to the meeting city?

Dr. Hugh A. Farris, Governor for the Maritime Provinces, stated that he had attended one of the courses, but that out of a group of fifteen only about three had come on to the Annual Session.

Dr. A. Comingo Griffith, Governor for Missouri, expressed the opinion that more members would attend the Annual Session if the graduate courses were given in cities nearer the seat of the Annual Session.

Dr. Charles F. Tenney, Governor for eastern New York, reviewed the experience of the New York Academy of Medicine in regard to its Postgraduate Fortnight. The annual Postgraduate Fortnight is usually devoted to some particular subject, such for instance as gastro-enterology, blood dyscrasias or endocrinology. By correlating the work and restricting it to a general subject, the course is very much more intensive.

He advocated that instead of utilizing many cities and scattering the registrants, all the Postgraduate Courses be given in one center, possibly changing the center from year to year. This would concentrate energy and add to the facilities of general contacts.

Dr. James G. Carr, Governor for northern Illinois, and director of the Postgraduate Course in Chicago, reported that several States had been represented in the registration, including Pennsylvania, Idaho, Tennessee, Michigan, Wisconsin, Nebraska, and others. Most of the registrants had intended to attend the Annual Session also. So far as specialties were concerned Dr. Carr advocated a more intensive study to determine what members desire and where they desire them. Those who pursued the courses at Chicago had expressed much pleasure and satisfaction concerning the course.

Dr. Louis H. Fligman, Governor for Montana, suggested the desirability of sending out the announcement of the Postgraduate Courses earlier in the year. Many physicians practice in smaller communities and have to make plans far in advance. They should be able to anticipate and arrange for attendance at these Postgraduate Courses longer in advance.

Dr. William B. Breed, Governor for Massachusetts, suggested that it might properly be made one of the functions of the Board of Governors to consider what the requirements are for admission to Associateship or Fellowship, because the Governors have a more intimate contact with the men who present themselves as candidates, and the suggestions presented by the Governors might be passed on to the Board of Regents and the Credentials Committee for consideration.

Chairman Cocke ordered that this be placed on the agenda for the next succeeding meeting of the Board of Governors, and that the Governors bring to that meeting specific suggestions.

Dr. Breed then asked the Board of Governors to view the commercial exhibits critically. He expressed himself as not being in sympathy with commercial exhibits, and expressed the fear that the College may be becoming too dependent upon income derived therefrom, because the exhibits may interfere with holding meetings of the College in some cities that lack facilities. He pointed out that the net income to the College at the preceding New York Session had been approximately $14,000.00 and somewhat over $11,000.00 at the current meeting. His only expressed objections to the commercial or technical exhibits referred to these considerations. However, Dr. Breed asked the Board to consider the possibility of adding a small scientific exhibit, such as conducted by the American Medical Association. He asked that the Board give this subject some thought and present suggestions at the next succeeding meeting.

Chairman Cocke reported that the Board of Regents had already instituted an investigation into all financial matters of the College, including exhibits and advertising, and would later have a report. However, Dr. Cocke requested that the Governors give the matter their careful thought and critical judgment, and bring up the subject again for discussion.

The Executive Secretary distributed complete copies of the financial statements of the College for the year 1938, for the information of the Governors, and offered to answer any questions concerning the same.

Adjournment:

(Signed)
Attest: E. R. LOVELAND,
Executive Secretary

MINUTES OF THE BOARD OF GOVERNORS

New Orleans, La., March 29, 1939

The second meeting of the Board of Governors of the American College of Physicians, held during the Twenty-third Annual Session, occurred on March 29, 1939, at the New Orleans Municipal Auditorium, with Dr. Charles H. Cocke acting as Chairman, Mr. E. R. Loveland acting as Secretary, and with the following present: Dr. Oliver C. Melson, Dr. Ernest H. Falconer, Dr. Fred M. Smith, Dr. W. S. Kerlin (representing Dr. J. E. Knighton), Dr. Henry R. Carstens, Dr. A. Comingo Griffith, Dr. Clarence L. Andrews, Dr. Charles H. Cocke, Dr. Julius O. Arnson, Dr. Alexander M. Burgess, Dr. Paul K. French, Dr. J. Morrison Hutcheson, Dr. Charles E. Watts, Dr. Walter E. Vest, Dr. Hugh A. Farris, Dr. Joseph Kaufman (representing Dr. Charles F. Moffatt), Dr. Fred W. Wilkerson, Dr. Fred G. Holmes, Dr. Lewis B. Flinn, Dr. Turner Z. Cason, Dr. James G. Carr, Dr. C. W. Dowden, Dr. Eugene H. Drake, Dr. Henry M. Thomas, Jr., Dr. G. W. F. Rembert, Dr. Louis H. Fligman, Dr. LeRoy S. Peters, Dr. Charles F. Tenney, Dr. A. B. Brower, Dr. Homer Rush (representing Dr. T. Homer Coffen), Dr. James F. Churchill, Dr. James J. Waring, Dr. Francis G. Blake, Dr. Robert M. Moore, Dr. Thomas Tallman Holt, Dr. William B. Breed, Dr. Warren Thompson, Dr. Leander A. Riely, Dr. Edward L. Bortz, Dr. John L. Calene, Dr. J. Owsley Manier, Dr. Louis E. Viko, Dr. Arthur Duryea, Dr. J. Howard Holbrook, Dr. Thomas Parran, Dr. Nelson G. Russell.

The Secretary read abstracted Minutes of the preceding meeting, which were approved as read.

Chairman Cocke reported that at a meeting of the Board of Regents on March 28 various matters referred by the Board of Governors had been taken under consideration. Furthermore, the Regents had instituted an intensive study of exhibits, fees and dues and all other matters affecting the finances of the organization. Dr. Cocke also reported that the Board of Regents had adopted a resolution requesting the Board of Governors to appoint a committee to act in an advisory capacity to secure information and to suggest regulatory principles concerning the postgraduate course program. This committee is to make a canvass and study of the situation with regard to location, time and other factors, with a view to making the courses further effective. The findings and recommendations of the committee shall be placed at the disposal of the Committee on Postgraduate Education of the College.

Dr. Thomas T. Holt, Governor for Kansas, reported that he had contacted all the members from his locality who had attended the Postgraduate Courses preceding the New Orleans Session, and had determined that they were all highly pleased and grateful for these courses. He advocated that the College should start a memorial library, having distinguished men and teachers give talks—such for instance as Dr. James B. Herrick on coronary thrombosis, as described in his earlier days—and having these talks recorded and placed in the College Library as memorials to these men.

Dr. J. Howard Holbrook, Governor for Ontario, expressed a deep interest in our program for postgraduate education, and predicted that physicians will not be going to Europe to the same extent for postgraduate work as in the past. He suggested that it be the duty of each Governor to see that the Associates in his territory shall be able to qualify as soon as possible for Fellowship. The Governors should always have available the full list of Associates, and they should encourage these men to pursue the Postgraduate Courses made available to them by the College. More Associates would undoubtedly pursue these courses if they were urged to do so by the Governors. He suggested that the Postgraduate Courses might very properly have as one of their chief objects that of qualifying Associates for Fellowship, and that the Credentials Committee should grant specific credit for attendance at Postgraduate Courses. Dr.

Holbrook said that the present is the opportune time for the College to make a real contribution in the field of Postgraduate Education.

Chairman Cocke reported that it is the custom of the Executive Offices to see that every Governor has a full and up-to-date list of all Fellows and Associates of the College, either through the Directory of the College or through additional reports following meetings of the Board of Regents when elections take place. He also said that the Regents were seriously considering the revision of the published requirements for Fellowship, coördinating the new requirements with those for certification by the national certifying boards. It is anticipated, he said, that in the near future certification by one of the national certifying boards shall be a requisite for Fellowship, though there will be other eligibility requirements.

Dr. Hugh A. Farris, Governor for the Maritime Provinces, reported that he had been requested to present a motion, recommending that the Postgraduate Courses be given at another time than the two weeks preceding the Annual Sessions; possibly following the meeting or, perhaps, in November of each autumn. Some members in his territory had contended that giving the courses before the annual meeting detracted from the meeting. Dr. Farris accordingly moved that the College present intensive Postgraduate Courses of one week following the meeting in the city where the meeting is held. The motion was seconded, and Chairman Cocke opened the question for discussion.

Dr. C. F. Tenney, Governor for eastern New York, pointed out that the Annual Sessions are always held in teaching centers, and that he felt the Postgraduate Courses could more advantageously be organized and given following the meetings. He favored a more closely organized unit with all courses being given in the one city under the general supervision of some distinguished man who had remained after the Session to take charge, supervise and coördinate the work. Dr. Tenney went on to describe the Postgraduate Fortnight of the New York Academy of Medicine. Their mornings are free; in the afternoon there are exhibits in the Academy, and these exhibits are one of the most valuable parts of the course. Lectures are given in the evening by men selected from all parts of the United States, Canada or Europe. Each year the Postgraduate Fortnight is devoted to some particular subject, rather than a diversity of subjects. He pointed out also the matter of expense. Members would have but one expense for railroad fare, if the courses were given in the Annual Session city. He also expressed approval of Dr. Holt's suggestion concerning Associates. He felt that their attendance at the Postgraduate Courses would mean far more than their preparation and submission of case histories and autopsies when coming up for Fellowship.

Dr. Fred M. Smith, Governor for Iowa, also was inclined toward feeling that perhaps the Board was overemphasizing the Postgraduate Courses for the Associates. He expressed his respect and confidence " for the man who can go on his own," and he said that the Associate who has to be carried along by the Governor will not make the sort of Fellow the College ought to have. The men who go farthest in medicine to a large extent are their own teachers, he said. They are influenced by meetings and contacts with men, but these things can be overdone. However, he expressed his approval of conducting the Postgraduate Courses following the Session in the same city.

Dr. Thomas Parran, Governor for the U. S. Public Health Service, pointed out that the motion before the Board might tie the hands of the Committee on Postgraduate Education as to the time and place for the courses, and asked Dr. Farris to consent to an amendment, namely, that the proposal of having Postgraduate Courses following the annual meeting be referred to the Committee on Postgraduate Education, rather than making it binding upon that Committee to schedule all of its courses as indicated. He pointed out that there were so many considerations that it did not seem proper for the Board to make a final decision at that time.

Dr. Farris accepted the amendment. Dr. C. F. Tenney pointed out that the Board might be overlooking the fact that in the cities where these meetings are held, the local men for a long time preceding and during the Session have an enormous amount of work to do on the meeting alone, and that all of these extra duties are added to their regular work. He thought it possibly would be a hardship to ask these same men to continue an additional week of postgraduate instruction.

The Secretary, Mr. Loveland, reported that for the preceding year when the Annual Session was held in New York, the Postgraduate Courses in such nearby cities as Boston and Philadelphia were better patronized because the men felt that they would see the best work being done in New York at the Annual Session, and that they would rather take their postgraduate work, therefore, in the nearby teaching centers. There had been fewer who registered for the Postgraduate Courses in New York City than in Boston and Philadelphia.

Dr. A. Comingo Griffith, Governor for Missouri, pointed out that the discussion thus far had shown the many angles to be considered, and no very definite scheme or plan should be adopted too quickly. He favored the Postgraduate Courses being held after the meeting, but that the Committee on Postgraduate Education might well schedule them in near-by cities. This would not necessarily increase the cost of transportation, because railroad tickets are usually good for thirty days, and by utilizing the nearby cities no undue burden would be put upon the local men in the meeting city.

Dr. Alex. M. Burgess, Governor for Rhode Island, urged greater coördination between the courses and through the succeeding years courses should be planned with relation to one another, and the programs coördinated from year to year. He suggested that some of the courses should be given in the autumn.

Chairman Cocke pointed out that the largest medical group in the south, the Southern Medical Association, always holds its annual meeting around the middle of November, and that this would have to be taken into consideration for any meetings scheduled in the autumn.

Dr. Walter E. Vest, Governor for West Virginia, recommended that the Committee on Postgraduate Education should schedule no courses that would interfere with the meetings of the Southern Medical Association.

Dr. Clarence L. Andrews, Governor for New Jersey, asked that the purpose of the Postgraduate Courses be clearly defined. Some men in his State had said they could not take the Postgraduate Courses and attend the Annual Sessions also. He felt that a greater premium should be placed upon attendance by the Associates at the Postgraduate Courses than at the Annual Sessions, and that certain credit for attendance at these courses be extended to all Associates when their credentials are presented for Fellowship.

Dr. J. Morrison Hutcheson, Governor for Virginia, referred back to the motion before the Board, and Dr. Farris informed him that the idea of the motion was that all Postgraduate Courses be scheduled following the meeting, and all other courses be suspended. Dr. Hutcheson reported that in his conversation with Associates, he had found that they felt the Postgraduate Courses in nearby medical centers had been most agreeable to them. He thought it a worthy objective to prevent any conflict of these courses with the annual meetings, and he was unfavorable to discontinuing all courses except those that could be given at the annual meeting city.

Dr. C. W. Dowden, Governor for Kentucky, expressed serious doubt whether the College should sponsor the courses at all. He felt that members may substitute attendance at the courses in place of going to the annual meetings, and that the annual meetings in themselves are the best postgraduate courses that members can obtain anywhere. Men interested in certain branches of medicine can go to the hospitals and see and hear what they want. The comparatively small number of members of the College attending these courses could attend any of the many other courses that

are springing up all over the country. He felt the College is doing entirely too much in this direction, and that these courses are detracting from the Annual Sessions.

Dr. Robert M. Moore, Governor for Indiana, reported that a postgraduate week had been initiated in Indianapolis some years ago, much on the same plan as the New York Postgraduate Fortnight. There is an intensive clinic presentation on all subjects, and outstanding men are brought to conduct the courses. He favored the continuation and promotion of postgraduate work. It is apparent that there will always be some conflicts and that attendance at the Postgraduate Courses may have some influence on the General Sessions; whether the Postgraduate Courses be given in the autumn or following the annual meetings, there is sure to be some influence on the enrollment of the annual meetings.

Dr. T. Z. Cason, Governor for Florida, reported that there is no medical school in the State of Florida, the nearest medical schools being located at Atlanta, New Orleans and Durham, N. C. For eight years the Florida State Medical Association has scheduled graduate courses for doctors of medicine, and Dr. Cason has been the Chairman. His experience had been that all graduate courses must be directed primarily to general practitioners. Figures cited showed that approximately 10 per cent of the members of the Florida State Medical Association availed themselves of these courses; men are brought in from outside of the State Medical Association for the program; the costs have been kept low, and a registration fee of only $5.00 has been charged. Heretofore, all the postgraduate work has been directed toward the general practitioner; the first half of the week was for the medical subjects and the second half for the surgical and obstetrical subjects. A new experiment was being tried the current year, with an intensive course on a single subject. He asked that the Committee on Postgraduate Education and the Board of Regents consider the plan of giving credit to Associates taking postgraduate work, suggesting that credit not necessarily be limited to those attending the Postgraduate Courses of the College.

Dr. Henry R. Carstens, Governor for Michigan, reported that in Michigan there is a similar program to that in Indiana and New York, only in a smaller way. It is directed toward the general practitioner, but there are also special courses.

Dr. A. B. Brower, Governor for Ohio, suggested that the Board of Governors should feel a personal responsibility, and that each Governor should send a letter outlining his ideas and suggestions to the committee that shall be appointed by the Board of Governors to survey the situation.

Dr. William B. Breed, Governor for Massachusetts, suggested that inasmuch as the motion had accomplished its purpose in creating wide discussion and review of the postgraduate situation, it be withdrawn without action.

Dr. Farris accepted the suggestion, as did also the seconder, and the motion was withdrawn.

Dr. Lewis B. Flinn, Governor for Delaware, "postgraduate education is an attempt to raise the caliber of medical practice throughout the country; first, perhaps, in regard to the members of the College and then the profession at large. The recent suggestions as far as certification by the American Board of Internal Medicine being made a requirement for Fellowship and the recent changes as far as hospital residencies are concerned go to this end. The Postgraduate Courses which have been discussed are more or less under the wrong momentum, and the details being discussed and worked out, in the wrong direction. Is there not another group, the forgotten group of doctors, the friends of doctors around the large metropolitan and teaching institutions in the more remote district of the country, particularly in the States and communities not in intimate contact with teaching institutions? It is a considerable problem to keep general practitioners and prospective internists abreast of things going on in medicine. I have two or three points for your consideration, but, perhaps, not for action at this time. First, the conduct of courses, such as Dr.

Cason of Florida suggested; second, country clinics, such as are being held in some States in the west and southwest. There is another problem which I should like to mention from a local standpoint in Delaware, namely, medical libraries. Until a few years ago, we had no medical library, but a number of members of the College, although not acting as such, were able to start a medical library, which has proved a splendid thing and a growing organization. Younger men, as they come along, are interested in reading and are trained to some extent to read. In the last two years the number of individuals in the community has doubled, and our efforts are now being directed toward carrying the service of a medical library, State medical library, current periodicals, etc., direct to the younger physicians particularly in the outlying districts. This is worth the effort, and may raise the standards of medical education, particularly in localities without facilities of teaching institutions."

Dr. Hugh J. Morgan, Chairman, Committee on Postgraduate Education: "Members of the Board of Governors, I am grateful for the opportunity of meeting with the Board to state very briefly the objectives that the Committee on Postgraduate Instruction has been concerned with in the two years I have been on the Committee. First, we felt that probably the most important things we had to deal with were in connection with postgraduate training for recent graduates in medicine. The matter of assistant residencies, residencies and Fellowships in medicine to the end that men can become trained in the field of general medicine and allied specialties are our objectives. We have been in difficult situations. There are many agencies interested in this problem. The American Medical Association, Council on Medical Education, the American College of Surgeons which has an intensive postgraduate program, and now ours, as a third major organization.

"In looking for the place to get into this field to do effective work, action has been deferred; as to what to do and where to do it. Even if one knows what one would like to do, he has to determine what places are available where recent graduates can go to get the training if they want to go into the field of Internal Medicine. That part of the problem is one of fact-finding. This is being done by the Council on Medical Education and Hospitals of the American Medical Association. We wonder if we could do it better or they could do it better. There is an Advisory Council on Medical Education, Hospitals and Licensure going into existence. We are concerned with this. That is one phase of the Committee's activities not touched upon in the discussion here, which is an important phase. This has to do with the recent graduates and potential members of the College.

"The other main interest of the Committee has been the subject of discussion here today. I think the divergent points that have been expressed here give an excellent idea how difficult it is to proceed in this field. It is important for us to make up our minds as to what the personnel will be. What group are these courses for, anyway. The College of Physicians is going to organize courses, for whom? Our idea is for our own members or potential members. We feel we have no concern in providing courses for general practitioners or for people interested in specialties not related to our own interests. If they are to be given for the College membership or potential members, that somewhat limits the field of our endeavor. We already give, in our annual meetings, one of the best postgraduate assemblies in the country, if not the best; certainly, in the field of general medicine. If our policies in the last two years, in trying to have general courses, has proved unsound. then we should throw that overboard and direct our attention in the courses of medical specialties.

"The question of time that should be put in our courses and when they should be given; their relation to the annual meeting of the College; the geographical distribution of centers in which to be given; all are points discussed here. It is very pertinent that the idea has been raised that these courses should not be given at all.

Against that is the idea that they are so important that we should employ disciplinary measures to force attendance.

"I think on behalf of the Committee that has been concerned with this problem for two years, I would like to say most that I am personally, and I am sure the Committee feels the same, deeply grateful for this Board interesting itself in this problem. We certainly have needed aggressive interest in considering this problem, in regard to just such questions as have been discussed here today. I think it is an important thing for the future that the Board of Governors will have a Committee to examine these questions and waive pros and cons and sift out of such facts as you are able to assemble, what would seem to be the wisest policies in regard to these courses. I think it is certainly going to mean that the Governors are going to have a viewpoint and I think it is an excellent thing, from the point of view of the College as a whole."

On motion by Dr. A. Comingo Griffith, seconded and regularly carried, it was RESOLVED, that the Board of Governors authorize a Committee on Survey of Postgraduate Education, the Committee to be appointed by the Chairman.

Chairman Cocke appointed Dr. Henry M. Thomas, Jr., Governor for Maryland, as Chairman; Dr. James J. Waring, Governor for Colorado; Dr. Edward L. Bortz, Governor for Eastern Pennsylvania; Dr. James G. Carr, Governor for Northern Illinois; and Dr. Ernest H. Falconer, Governor for Northern California.

Dr. J. Owsley Manier, Governor for Tennessee, expressed the opinion that it will be difficult for this Committee to know what action it shall be best to take. He proposed that Dr. Brower's suggestion of a letter from each Governor to the Committee would be helpful. He, therefore, suggested that the Board of Governors instruct the Committee to communicate tentative plans to the individual Governors.

Dr. Thomas Tallman Holt, Governor for Kansas, suggested that each Governor canvass his State and find what the men want and report such findings to the Committee.

Dr. Walter E. Vest, Governor for West Virginia, spoke from the standpoint of the public health aspect, pointing out that this body had been considering postgraduate education from the Board's standpoint, and that those who need postgraduate education least get it; those who take the courses are those who, in the final analysis, need it least, and the College needs some way of reaching the men in the outlying districts who do not get postgraduate instruction.

Chairman Cocke stated that the usual reports on State and district meetings would have to be omitted because of lack of time, but that reports of these had been published from time to time in the "Annals." He asked the individual members of the Board to give some consideration to entrance requirements to the College. The Credentials Committee may circularize members of the Board to get their suggestions.

Mr. Loveland, the Executive Secretary, asked if the Board of Governors would express any sentiment about the place of the next annual meeting. He reported that invitations had been received from San Francisco, St. Paul, Buffalo, Cleveland and Boston for the 1940 Session, and from Kansas City for the 1941 Session. The meeting place is determined upon by the Board of Regents after careful consideration. He said that the two cities most seriously under consideration for 1940 were Boston and Cleveland. The American Medical Association will hold its 1941 Session in Cleveland.

Dr. A. B. Brower, Governor for Ohio, spoke in favor of the 1940 Session being held in Cleveland. He pointed out that the College had not convened there since 1927, and that inasmuch as Cleveland could not entertain the College in 1941, because of the meeting of the American Medical Association, Cleveland particularly wishes to concentrate on our meeting in 1940. He emphasized Cleveland's splendid physical equipment and geographical location. He also felt that hospital facilities are adequate, and that every coöperation would be received from the medical school, the local

Academy of Medicine and College members. The whole invitation had been carefully and fully discussed with the various members of the hospital staffs and teaching staffs, and full coöperation everywhere had been assured. Furthermore, the College membership in the Cleveland district has been greatly strengthened by the election of several of its outstanding internists, and that from every standpoint, the Cleveland invitation should be seriously considered.

Dr. William B. Breed, Governor for Massachusetts—"It seems that the turn of the wheel is up to Cleveland and Boston. The College met ten years ago in Boston. I should say that 1941 would be just as good a year for Boston. We would welcome you in either year. Apparently, 1941 is out for Cleveland. I think that our invitation would hold just as enthusiastically in 1941 as in 1940."

On motion by Dr. A. M. Burgess, seconded by Dr. A. C. Griffith, and unanimously carried, it was

RESOLVED, that the Board of Governors recommend to the Board of Regents the selection of Cleveland for its 1940 Session.

Following several general announcements concerning meetings, the Board adjourned.

Adjournment:

(Signed)
Attest: E. R. LOVELAND,
Executive Secretary

OBITUARIES

DR. ALEXANDER JOHN MACKENZIE, V.D., B.A., LL.D., M.B., F.A.C.P., Lieut.-Colonel (ret.) 48th Highlanders of Canada

Dr. A. J. MacKenzie, President of the Ontario Medical Association, died at his home in Toronto, March 3, 1939, after a short illness.

He became a Fellow of this College in 1926 and prized highly his association with the College.

The second son of the late Peter MacKenzie, federal member for South Bruce, he was born at Lucknow, Ont., 66 years ago. Entering University College in the University of Toronto he studied political science and law, with a group of men who became prominent in political life. He took his Arts degree in political science, graduated in law and in medicine. During his course he took an active part in athletics and for several years played an outstanding game in intercollegiate Rugby. His interest in these activities made him a valued member of the Athletic directorate of the university.

He spent a year as intern in the Toronto General Hospital and in a very short time began practice in Toronto. For nearly thirty-five years he taught in the Faculty of Medicine of his university, and for twenty years was the head of one of the medical services in St. Michael's Hospital, where he gave freely of his time and energy to both university and hospital work, rarely missing a day in his wards.

Soon after graduation he was appointed Physician to Upper Canada College, and two generations of men had the advantage of his supervision and advice in sickness and in health. For over thirty years too he was medical officer of the 48th Battalion (Highlanders) rising to the rank of Lieut.-Colonel in that unit in 1917. The 15th Battalion C.E.F. was recruited from the 48th militia, and as M.O. to the 15th Battalion, he proceeded overseas with the first contingent, spending the first winter amidst the discomforts of Salisbury Plains, and then to France where he saw his men falling about him during the first murderous gas attack launched by the Germans at Ypres in April 1915. Those who survived are proud to recall his devotion to his comrades during the trying days which followed. Later in England, he was O.C. Princess Patricia's Red Cross Hospital at Ramsgate, and on his return to Canada was for some time O.C. Military Hospitals in M.D. No. 6 (Halifax). Later he was consultant in medicine M.D. No. 2. His Medals and decorations were the 1914–15 Star, The British War Medal, the Victory Medal and the V.D., the Colonial Auxiliary Forces Officers Decoration.

A charter member of the Academy of Medicine, Toronto, Dr. MacKenzie served actively on many committees, was chairman of the Section of Medicine in 1922, in 1926 became President, and for seven years served on

council. For many years he was active in the Ontario Medical Association. As Counsellor for District No. 11 he did most valuable work for his profession, devoting much time to his important office; this led him into the administration of medical relief when it was inaugurated in the province. His wise counsel and advice will be much missed by those who have the duty of carrying on this work for the Ontario Medical Association. Elected to the presidency of the Association last year he entered into the duties of his office well equipped in every way to be the guiding hand in its many activities, and he spared neither time nor effort to ensure the success of its undertakings.

He will be sorely missed. He was beloved of his students and no one in the medical profession could be held in greater respect. A medical statesman of the first order he was ever ready to assist in any movement which would make the practice of medicine more generally serviceable to the public.

Besides two brothers and two sisters he is survived by his widow, the former Norma Sutherland, daughter of Hon. R. T. Sutherland, a Justice of the High Court of Ontario, and formerly a Speaker in the House of Commons.

Following a private service in his late residence his body lay in state in St. Andrew's Church until the funeral service at 2 p.m. on Monday, March 6, which was attended by hundreds of his friends from all walks of life, with special representatives from the many organizations with which he had been long associated. Dr. MacKenzie loved the simple things of life and the funeral service was typical of his disposition. The ceremony was short and minus an address of eulogy.

Dr. MacKenzie was borne to his grave in Mount Pleasant Cemetery where, under the flag he had so well served, he was laid to rest with the lament of the bagpipes of his forbears, and the Last Post of the bugler of his well loved regiment.

J. H. Elliott, M.D., F.A.C.P.,
Toronto, Ontario, Canada.

DR. ROBERT LEE FELTS

Dr. Felts was born in York County, South Carolina, November 15, 1870. After graduating from the Carolina Academy, he began pharmaceutical studies, receiving the Ph.G. degree from the Maryland College of Pharmacy and his M.D. degree from the University of Maryland School of Medicine in 1898. His postgraduate studies embraced courses in pediatrics in 1924 and in internal medicine in 1922 and 1926.

During the Spanish American War, he served in the Medical Corps of the Fifth Maryland Regiment, where first began his interest in typhoid fever, which became one of his dominant medical interests, by reason of his wide knowledge of the disease then so prevalent. He was stationed in Manila in the Philippine Islands from 1898 to 1902, and was commanding surgeon at

Fort Sam Houston, Texas, from 1902 to 1906. He settled in Durham in private practice in 1907, and from then until illness incapacitated him, was one of the leading internists of his community.

For many years he was Chief of the Medical Staff of Watts Hospital, Durham, a member of the visiting medical staff of Duke Hospital; Secretary of the Durham County Board of Health from 1925 on, member and ex-President of the Durham-Orange County Medical Society; member and ex-Counselor of the Sixth District of the N. C. State Medical Society; member of the Southern Medical Association; member of the American Medical Association; and Fellow of the American College of Physicians since 1931.

At the time of his death, at his home, from coronary thrombosis, May 27, 1939, he was senior attending physician at Watts Hospital.

His publications on the subjects of pyelitis and pregnancy; neurological sequellae of influenza, chylothorax, acute Hodgkin's disease, and purpura hemorrhagica, indicate the catholicity of his interests.

In June 1904, he married Miss Elizabeth Person Kearney, who died in 1925, surviving which marriage are two daughters, Mrs. Virginia Felts Pickard and Mrs. George L. (Elizabeth Felt) Lyon. November 15, 1928, he married Miss Jessie Alexander, from which union a son survives, Robert Lee Felts, Jr.

A man of very dominating personality and strength of character, Dr. Felts owed his position in his community to those qualities of character and honesty which animated all of his dealings with his fellowman. He was a member and past President of the Kiwanis Club; originated and was Chairman of the Durham Community Chest, 1923–1926; a member of Trinity Methodist Church, and a member of the Board of the American Red Cross. His interest in politics was active, but he still found time in a busy life for constant study and reading of medical literature. His passing leaves a void in the medical circles of his community.

CHAS. HARTWELL COCKE, M.D., F.A.C.P.,
Governor for North Carolina.

DR. SAMUEL ROBERT SLAYMAKER

Dr. Samuel Robert Slaymaker died on May 3, 1939, of carcinoma of the pancreas. Dr. Slaymaker was born in 1864 and received his degree in medicine from Rush Medical College in 1892. He spent his entire professional life in Chicago, where he built up a large practice. For most of his time he was connected in some capacity as a teacher in the Medical Department of his Alma Mater, and for many of his later years he held the title of Clinical Professor of Medicine. He was Associate Attending Physician at the Presbyterian Hospital for many years. He also served as a member of the Attending Staff at the Cook County Hospital for a period of some twenty years. His last term in the Cook County Hospital was

marked by his serving as Chief of the Department of Medicine. For many years he was Attending Physician of the Washington Boulevard Hospital, where he also served as President of the Staff.

Dr. Slaymaker was President of the Chicago Society of Internal Medicine during 1922 and 1923. He was one of the founders of the Chicago Institute of Medicine and took an active interest in this work. He was a member of the Chicago Medical Society for a long period, and was a Fellow of the American Medical Association. He was also a member of the Illinois State Medical Society, the Chicago Pathological Society, the Chicago Society of Industrial Medicine, the Chicago Society of Medical History and an Associate of the American College of Physicians. He was an active member of St. Barnabas Episcopal Church.

The death of Dr. Slaymaker removes from our midst one of the best beloved men in Chicago. Through his contacts with patients, with his fellow practitioners and medical students, Dr. Slaymaker had acquired an exceptionally wide acquaintanceship. Wherever he was known he was accorded not only respect but affection. His students and internes with whom he had contact were especially devoted to him and will retain a grateful memory for the opportunity of having served with one so successful in diagnosis, so accurate in treatment, and so considerate in the care of his patients. Dr. Slaymaker's work was excellently done. His memory will be cherished as much for his genial, kindly personality as for the work he did in professional ways.

JAMES G. CARR, M.D., F.A.C.P.,
Governor for Northern Illinois.

DR. BYRON HUBBARD JACKSON

Dr. Byron Hubbard Jackson of Scranton, Pennsylvania, a Fellow of the American College of Physicians since 1934, died May 16, 1939.

Dr. Jackson was born in Kingston, Pa., September 22, 1873, and graduated from the Baltimore Medical College in 1898. He was engaged in general practice until 1908, from which time he followed the specialty of roentgenology exclusively.

Dr. Jackson held the following positions: Roentgenologist, State Hospital of Northeast Pennsylvania, 1908–26; Roentgenologist, Moses Taylor Hospital, 1908 to date; Roentgenologist, Hahnemann Hospital 1917–33; Roentgenologist, West Side Hospital, 1917 to date; Roentgenologist, St. Mary's Kellar Memorial Hospital, 1920 to date; Roentgenologist, West Mountain Sanatorium and Pennsylvania State Tuberculosis Clinic, 1916 to date.

Dr. Jackson was the author of several published papers.

Dr. Jackson was a member of the Lackawanna County Medical Society, The Pennsylvania State Medical Society, American Medical Association,

American Roentgen-Ray Society, Radiological Society of North America (ex-President), Pennsylvania Radiological Society, Central New York Roentgen-Ray Society, Philadelphia Roentgen-Ray Society, Lehigh Valley Medical Society, American College of Radiology (Fellow), Royal Society of Medicine of London (honorary), and a Fellow of the American College of Physicians since 1934.

Dr. Jackson was one of the leading roentgenologists of the State of Pennsylvania. He held the respect of a widespread circle of friends. His passing is a loss, not only to his family and his many friends, but to the medical profession in the section in which he resided.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania.

DR. GEORGE CHARLES HENRY FRANKLIN

Dr. George Charles Henry Franklin, Lieutenant Colonel, Medical Corps, U. S. A., died suddenly following a heart attack April 23, 1939, at Fort Leavenworth, Kansas.

Colonel Franklin was born in California, November 5, 1886. He graduated in medicine at Cooper Medical College, May, 1912, after which he served for a year as intern and another year as resident physician in Mt. Zion Hospital, San Francisco, California. He entered the Medical Corps of the Army August 10, 1917 and was promoted through successive grades from First Lieutenant to that of Lieutenant Colonel on April 1, 1937. During the World War he was with the A.E.F. in France from May, 1918, to June, 1919.

This medical officer was an outstanding laboratory specialist. He was quiet, unassuming, earnest, sincere and a hard worker. He was assigned for the usual tour of an army officer of from two to four years to a number of important army stations. He served in Panama, 1928–31, as chief Bacteriologist of the Board of Health. After this he was given a year of detached service to attend the School of Tropical Medicine in London. On completion of the prescribed course he received the degree of D.T.M. and H. His next duty was that of instructor for a period of four years in Medical Entomology and Helmintology at the Army Medical School, Washington, D. C. His last assignment was chief of the laboratory service, Station Hospital, Fort Leavenworth, Kansas.

Colonel Franklin became an Associate of the American College of Physicians during 1936, and was advanced to Fellowship at the New Orleans Session, March 26, 1939.

JAMES C. MAGEE, Major General, U. S. Army,
The Surgeon General.

DR. MARY O'MALLEY

Dr. Mary O'Malley, nationally-known psychiatrist and neurologist and at one time the only woman clinical director for mental diseases in the United States, died January 30, 1939, at her home, 35 Brantford Place, Buffalo, N. Y. She had been ill for the last six months.

Prior to her retirement three years ago, Dr. O'Malley was in charge of more than 1,500 women patients at St. Elizabeth's Hospital, Washington, the largest institution for mental cases conducted by the federal government. She was the first woman physician accepted at St. Elizabeth's and held the position of clinical director for more than a quarter of a century.

Dr. O'Malley served as the head of many medical, neurological and pathological organizations and was president of the Medical Women's National Association in 1933. She contributed numerous scientific articles and in 1931 was a delegate to the International Medical Women's Association at Vienna and the International Neurological Congress at Berne.

Dr. O'Malley was born in Orleans County, daughter of Bridget Whalen O'Malley and Michael O'Malley, justice of the supreme court of New York State. Dr. O'Malley was educated in the vicinity schools and the University of Buffalo. She was graduated in medicine in 1897 and served her internship at the Sisters of Charity Hospital here.

Upon completing her internship, Dr. O'Malley was appointed woman physician at Binghamton State Hospital, where she remained for seven years until going to St. Elizabeth's Hospital where she made a brilliant record.

Dr. O'Malley is survived by her sisters, Anna and Margaret O'Malley of Buffalo, and one brother, John O'Malley of Barker. She became a Fellow of the American College of Physicians in 1928.

NELSON G. RUSSELL, M.D., F.A.C.P.,
Governor for Western New York.

DR. ALFRED FRIEDLANDER

A host of friends, as well as all of the doctors of Cincinnati, deeply mourn the recent passing of Dr. Alfred Friedlander, on May 28, 1939. His close association with the Medical College ever since his graduation from this school, his wide interests, his genial personality, and his wise counsel, placed him on the altar of medical fame. More recently his appointment as Dean of the University of Cincinnati Medical College again demonstrated his unusual ability in not only medical, but executive matters. Dr. Friedlander's background was one of fine preparation for the profession which he followed so successfully for many years. He received his B.A. degree from the Harvard University in 1892, and his M.D. degree in 1895 from the University of Cincinnati College of Medicine. He pursued for several years postgraduate study in pathology and medicine in the leading

universities of Germany and Austria. He served his internship at the Cincinnati General Hospital. His War record as Major in the Medical Corps, and Chief of the Medical Service, Post Hospital, Camp Sherman, was an enviable one.

At the time of his death, Dr. Friedlander was Professor of Medicine, University of Cincinnati College of Medicine, and Chief of Staff of the Chronic Disease Hospital. He was also Attending Physician at the Cincinnati General Hospital.

Dr. Friedlander was the author of a book on hypotension, contributed a chapter in Abt's "Pediatrics," and a chapter in Blumer's edition of Forcheimer's "Therapeusis of Internal Diseases." He was the author of many published articles.

Dr. Friedlander was a member of the American Pediatric Society; Ohio State Medical Association; Cincinnati Academy of Medicine, American Medical Association; and a Fellow of the American College of Physicians since 1931. In his passing the American College of Physicians loses one of its most valuable members.

JULIEN E. BENJAMIN, M.D., F.A.C.P.,
Cincinnati, Ohio.

DR. PAUL EUGENE LINEBACK

Dr. Paul Eugene Lineback, aged 59, died February 28, 1939, after a short illness. Dr. Lineback, a native of Winston-Salem, N. C., graduated from the Drake University College of Medicine, Des Moines, Iowa, in 1911. In 1912 and 1913 he served as Professor of Anatomy at Drake University College of Medicine, and in 1914 practiced at Anaconda, Montana. Later he did postgraduate work at Harvard University Medical School and was one of two southerners selected to contribute to the Carnegie Institute on anatomy. Dr. Lineback received an honorary lectureship at the University of London and also did postgraduate work at the Colonial Institute, Amsterdam, Holland. He was a member of the faculty of the University of Chicago from 1917 to 1922, later becoming associated with the Emory University School of Medicine as Professor of Microanatomy, which position he held at the time of his death. He was the author of a number of published articles, and co-author of "Anatomy of the Rhesus Monkey." He was a member of the American Association of Anatomists, Fellow, American Association for the Advancement of Science, and Fellow, American College of Physicians since 1927. Dr. Lineback was a superb teacher, a valuable leader in the medical school and a man of sterling personal character.

GLENVILLE GIDDINGS, M.D., F.A.C.P.,
Governor for Georgia.

DR. FRANK PARSONS NORBURY

Dr. Frank Parsons Norbury (F.A.C.P.), Jacksonville, Ill., died suddenly at his hospital for nervous and mental diseases at Jacksonville, March 14, 1939. A few years ago he developed Parkinson's disease, following an attack of poliomyelitis, from which he gradually became physically impaired, but had been able to attend patients at his institution during part of this time.

Dr. Norbury was born at Beardstown, Ill., August 5, 1863. After graduating from the Beardstown High School, he entered Illinois College, but before graduation transferred to the Medico-Chirurgical College of Philadelphia, 1886–87, and again transferred to the Long Island College of Medicine, from which he graduated with the degree of Doctor of Medicine in 1888; he later was honored with an A.M. degree from Illinois College in 1903.

Dr. Norbury formerly was Resident Physician, Pennsylvania Institution for Feeble Minded Children, 1888; Assistant Physician, Illinois Central Hospital, Jacksonville, 1888–93; Physician to Oak Lawn Retreat, 1896–1900; Superintendent and Medical Director, Norbury Sanatorium, Jacksonville, 1901–09; Superintendent Kankakee State Hospital, 1909–11; Alienist, Board of Administration of Illinois, 1911–13; Medical Director, Norbury Sanatorium, 1913 to time of his death; also at time of his death, Consulting Neuropsychiatrist, Wabash Employees' Hospital; Secretary, Section of Neurology and Medical Jurisprudence, 1893–94, and Member of the House of Delegates of the American Medical Association, 1904; Past President, Morgan County Medical Society; Member, American Psychiatric Association; Past President and Secretary, Mississippi Valley Medical Association; Professor of Internal Medicine, St. Louis College of Physicians and Surgeons, 1895–96; and Professor of Nervous and Mental Diseases, Keokuk (Iowa) Medical College, College of Physicians and Surgeons, 1904–08; Acting Medical Director of the National Committee for Mental Hygiene during the World War.

Dr. Norbury entered the practice of medicine at a time when there was limited clinical knowledge of the care and treatment of nervous and mental diseases. At the time he began his work in the State institutions, they were considered only a place of confinement where patients might be kept who were unable to be cared for in their homes. He advocated more careful study with case histories and more definite clinical diagnosis, that these cases might have proper treatment and be restored to their families.

At that time, there were no laboratory aids to diagnosis, so that clinical knowledge of the patient was obtained only by long hours of personal effort. When he began his administration, little was known of the modern knowledge and treatment of cases of paresis, which filled the greater percentage of beds in our State hospitals. He clearly saw these conditions and it was his pioneering efforts that have brought about the modern change in the institutions of the State.

As a Consultant, he was well known to the public and the medical profession of central Illinois for a quarter of a century. His personal and ethical relations with the medical profession have always been of the highest character, and for these attainments he will always be remembered by those who knew and loved him.

Dr. Norbury had been a Fellow of the American College of Physicians since 1917.

SAMUEL E. MUNSON, M.D., F.A.C.P.,
Governor for Southern Illinois.

DR. JOSEPH CARL KAMP

Dr. Joseph Carl Kamp, F.A.C.P., Casper, Wyoming, died on May 13, 1939, at the Scripps Metabolic Clinic, La Jolla, California, following an illness of several months' duration. He was 60 years of age.

Dr. Kamp was born on September 7, 1879, near Cologne, Germany, coming to America at an early age. His primary education was received in the Parochial and Public Schools and Saint Benedict's College of Newark, New Jersey, after which he entered the Medical Corps of the United States Army, serving through the Spanish-American War and later being stationed at Fort Riley, Kansas and Fort Douglas, Utah. He attended the University of Utah and then the Denver and Gross College of Medicine, later merged with the University of Colorado, receiving the degree of Doctor of Medicine in 1909.

The following year he entered the practice of medicine at Casper, Wyoming. Postgraduate medical study was received at the Chicago Polyclinic (1915), New York Postgraduate Medical School (1922, 1923, 1924, 1925, 1926, 1934), Santa Barbara College Hospital (1927), Mayo Clinic (1928), and the University of Vienna (1936). He became an Associate of the American College of Physicians in 1924 and was elected to Fellowship in 1929, being the first Wyoming physician to attain this distinction.

He was a member of the American Medical Association, the Wyoming State and Natrona County Medical Societies and a staff member of the Natrona County Memorial Hospital, and held a commission of Major in the Medical Reserve Corps of the United States Army.

Dr. J. C. Kamp was an outstanding individual. Prominent in his profession in the state of Wyoming and interested in civic and community problems in Casper, he will forever be cherished in memory by those who knew him.

GEORGE E. BAKER, F.A.C.P.

DR. JOHN ANDREW MURPHY

Dr. John Andrew Murphy died June 13, 1939 at his home 313 Dickinson Avenue, Swarthmore, Pennsylvania. Dr. Murphy was 59 years old.

Dr. Murphy was a graduate of the University of Pennsylvania School of Medicine, 1903; Assistant Professor of Clinical Immunology, University of Pennsylvania Graduate School of Medicine; Associate, Asthma Clinic, Presbyterian and Abington Memorial Hospitals and Germantown Dispensary and Hospital.

During the World War, he served in France for a year and a half, retiring from the army with the rank of lieutenant colonel. He was past commander of the Ainsworth Post, American Legion, Swarthmore.

Dr. Murphy was a member of the Philadelphia County Medical, the Association for Study of Allergy, and the Society for the Study of Asthma.

Dr. Murphy was elected an Associate of The American College of Physicians in 1925.

He is survived by his widow, Elizabeth; a son, Francis Blake Murphy, and a daughter, Mrs. Henry Hagert.

EDWARD L. BORTZ, M.D., F.A.C.P.
Governor for Eastern Pennsylvania.